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CLINICAL NOTES.*

(1) INTERMITTENT FEVER IN INFLUENZA SIMULATING MALARIAL FEVER. (2) GRAVE MALARIAL FEVER WITH FEW PARASITES IN THE PERIPHERAL CIRCULATION. DANGERS OF THE INTRAVENOUS INJECTION OF QUININE.

By William Sydney Thayer, M. D.,

Associate Physician, The Johns Hopkins Hospital, Baltimore.

Every one who has observed much malarial fever is familiar with the fact that well-marked paroxysms may occur with the presence of very few parasites in the peripheral circulation. (a) This is not uncommon in mild tertian infections. (b) Furthermore, it is observed at the onset of mild and even of more or less serious æstivo-autumnal fever, especially during the period of the paroxysm. The cause of this is evident enough when we remember that the sporulation of the parasites which immediately precedes and accompanies the paroxysm in both tertian and æstivo-autumnal fever, occurs, especially in capillaries of certain of the internal organs, particularly in the spleen and bone marrow. In most mild cases of æstivo-autumnal fever, it is rather difficult to find sporulating parasites in the peripheral circulation. (c) The same condition, *i. e.*, well-marked fever with few or no parasites demonstrable in the peripheral circulation, is seen in both tertian and æstivo-autumnal infections, but, especially in the latter, where quinine has been given in insufficient doses early in the attack.

In most patients, careful examination of blood reveals parasites within the twenty hours succeeding the paroxysm, and, even in the absence of parasites, the diagnosis is usually sufficiently clear through the history of the case and the physical appearances, in connection with the condition of the blood which shows usually (1) leucopenia, (2) pigment-bearing leucocytes, (3) a relative increase in the large mononuclear leucocytes.

Nevertheless, it is well known that there are occasional cases in which, without splenic puncture, a diagnosis can be reached only by the therapeutic test. These cases are not common and,

*Remarks made before the Johns Hopkins Hospital Medical Society on Oct. 17, 1909.

in a community where a study of blood is a part of the routine examination, as it is here, where one usually waits for the demonstration of parasites before the administration of quinine, it is easy to lay too much stress on the negative results

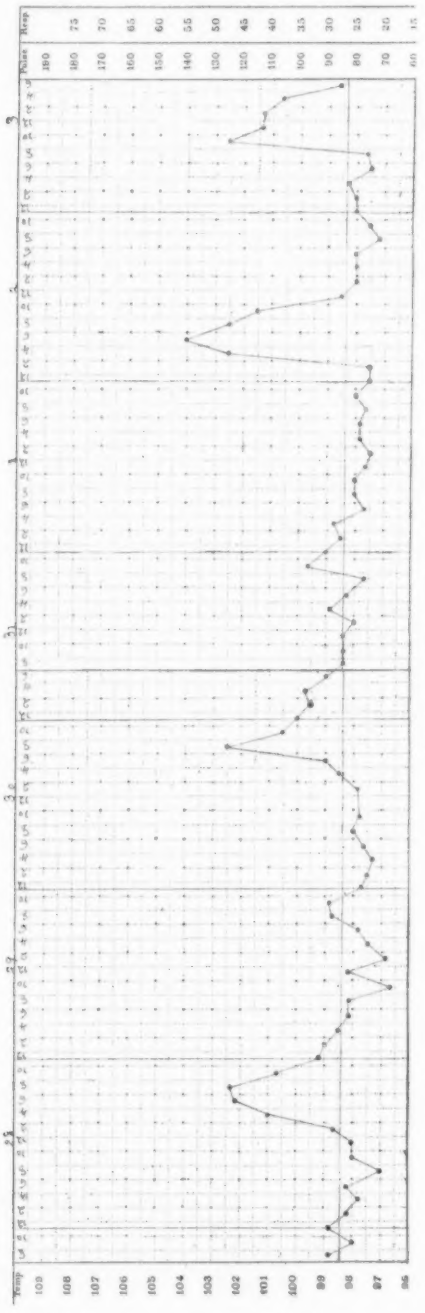

CHART I.—INFLUENZA.

of such examinations and to forget that grave and even pernicious malaria may occur in an individual with so few parasites in the peripheral circulation as to deceive even the skilled observer on repeated examinations.

On the other hand, however, 'tis very important to remember that certain other infections may give rise to paroxysms which, intrinsically, and in the character of their periodicity, may closely simulate malaria.

The paroxysms of streptococcus, pneumococcus and gonococcus septicæmia are usually distinguishable by the irregularity, often the great frequency of the paroxysms, and the short duration of the individual access. The paroxysms occurring in tuberculosis may often suggest malaria, but are usually readily distinguishable. In the experience of the writer, influenza is the malady which gives rise to those forms of intermittent fever which most closely simulate malarial paroxysms. Of the four cases of which we shall speak this evening, two are examples of influenza simulating malaria; two are instances of grave malarial fever with a remarkable paucity of parasites in the peripheral circulation.

CASE I.—*Influenza—Tertian Paroxysms Simulating Malaria.* The first chart, which has already been published in my "Lectures on the Malarial Fevers," * is that of a woman, E. D., aged 29, who was a patient on Ward "G" of the Johns Hopkins Hospital. The chart, as you will see, shows a febrile paroxysm beginning between 2 and 4 p. m., on the 28th of January and lasting 12 hours. This was succeeded on the 30th by a similar paroxysm beginning about two hours later and lasting about the same length of time. The patient came from a malarious district and we naturally suspected a tertian infection. On the first of February, however, there was no rise of temperature and on the 2d and 3rd, sharp elevations occurred, one between 12 and 2 in the morning and the other between 8 and 10 on the following morning. These latter paroxysms, of course, would be sufficient, on examination of the chart alone, to render the diagnosis of malaria improbable.

Now, this patient complained of coryza and cough with a greenish purulent expectoration, and showed the signs of a general bronchitis. Examination of the blood revealed no malarial organisms, and a leucocytosis of 17,000. Influenza bacilli were cultivated from the sputa and the patient recovered without relapse, and without the administration of quinine.

CASE II.—*Influenza—Remittent and Intermittent Fever Simulating Malaria.* The second chart is that of a patient whom I saw in February, 1907, with Dr. Friedenwald. As you will see, there is a period of four days of irregular fever, followed by three quotidian paroxysms, each beginning between 8 and 10 in the morning and closely simulating paroxysms of a regularly intermittent malaria. One might well have fancied that the case represented one of infection with mutiple groups of parasites which, under rest in bed, had gradually given way until the effects of two strong groups became clearly evident.

The patient, however, was a boy of about 17 who had been ill for about three or four days before the beginning of the chart, complaining of coryza and cough with purulent expectoration and the general symptoms of influenza which was prevalent at the time. From the onset, he had been treated with quinine, gr. iii. (0.2 gm.) every four hours. Well-marked chills continued for nearly a week after the onset of treatment. The blood showed no malarial parasites.

I saw the patient first on the 14th of February, at which time he showed a general bronchitis. Quinine was omitted and aspirin, gr. v. (0.325 gm.) every four hours ordered. Cultures from the sputa showed *B. influenzæ*.

The point of special interest in this case would appear to be the sharpness of the paroxysms which were associated with definite

* Thayer, W. S.: Lectures on the Malarial Fevers, New York, D. Appleton & Co., 1897.

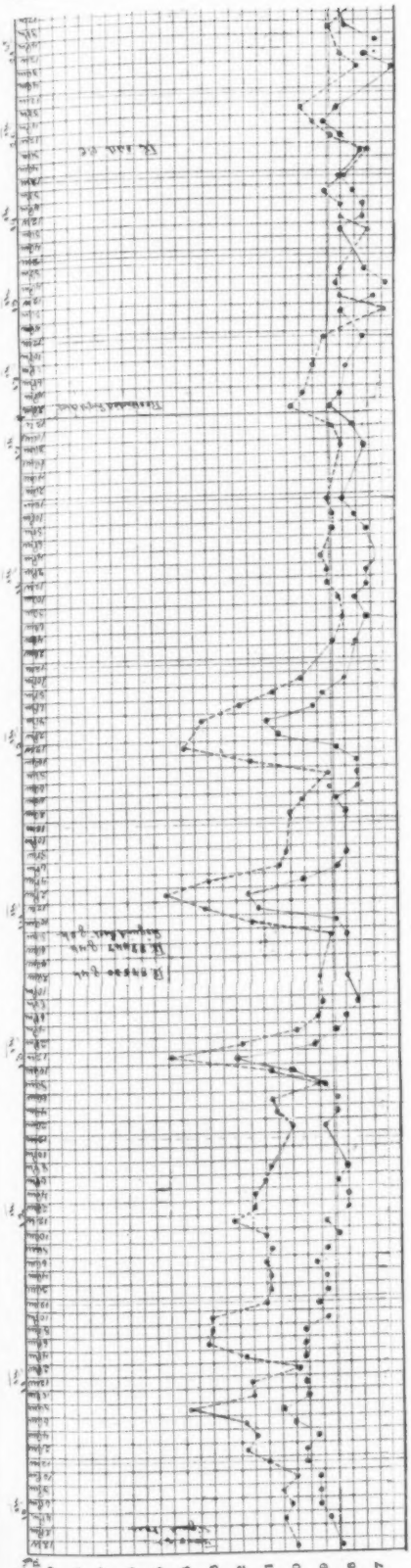

CHART II.—INFLUENZA.

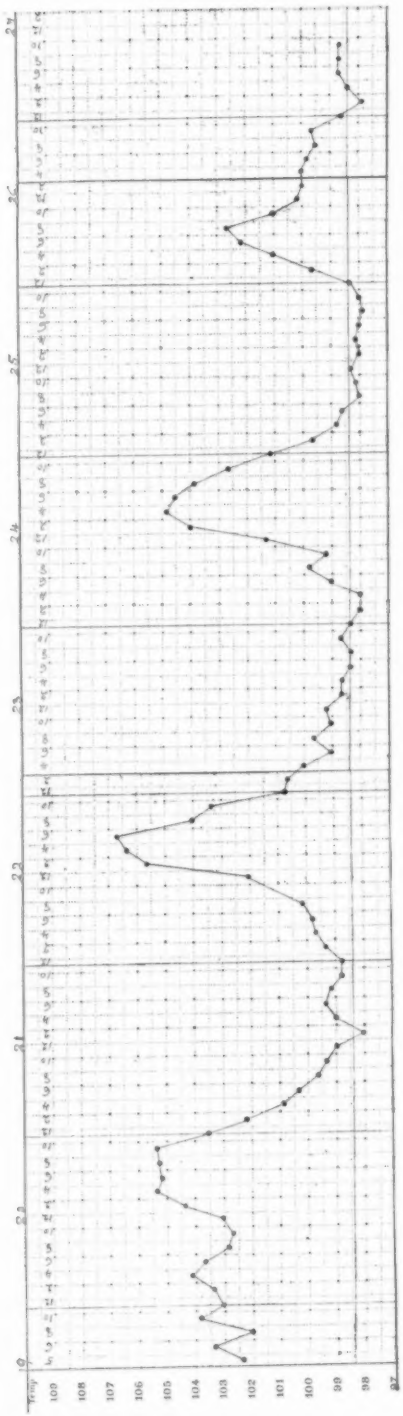

CHART III.—MALARIAL FEVER, ESTIVO-AUTUMNAL TERTIAN.

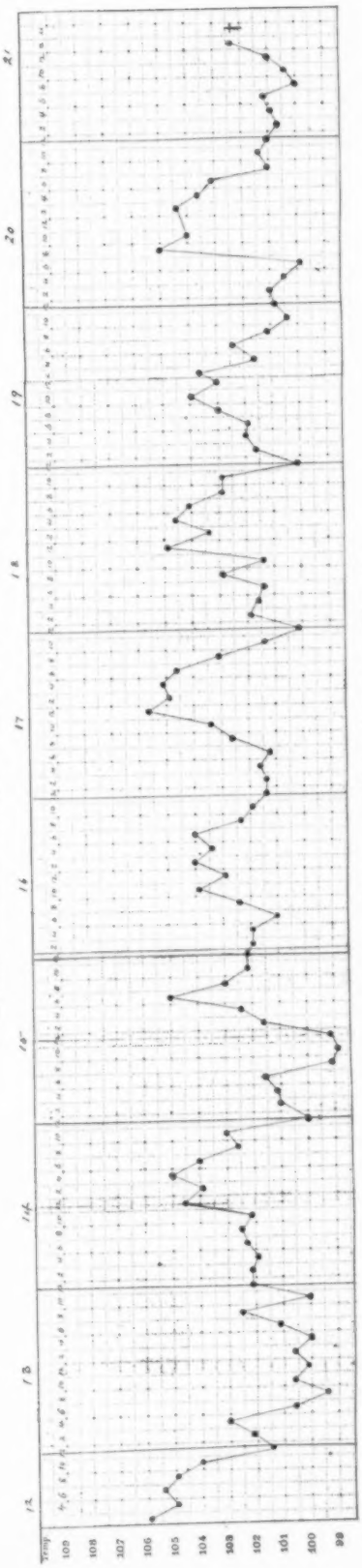

CHART IV.—MALARIA.—ESTIVO-AUTUMNAL TERTIAN.

chills, and the regularity of their onset in the morning hours, as is common in malaria.

CASE III.—*Intermittent Fever of the Type of Aestival Tertian. No Parasites Demonstrable in the Peripheral Circulation. Immediate Disappearance of Fever under Quinine.* The third chart that I would show you presents a rather different appearance. As you will see, there is continued fever on the 19th and 20th of October, the temperature reaching a sub-normal point on the 21st. This is followed by sharp paroxysms on the 22d, 24th, and 26th, the paroxysms beginning in the early morning hours and lasting nearly 24 hours. The chart is typical of aestivo-autumnal tertian fever.

The patient was a medical student of 28. He had been in a malarious district and, two days before admission, had begun to complain of general malaise and on the day preceding admission, of fever. On the day of admission, the 19th of October, he had taken three doses of quinine, how much is not known. On entrance, the temperature was 102.4° F. at 5 P. M., the pulse 80, respiration 24. There was nothing striking on physical examination of the patient beyond a palpable spleen which extended 3 cm. below the costal margin. The examination of the blood was negative; no parasites and no pigment were seen and the leucocytes were 6400 per cmm.

Oct. 20. The temperature remained elevated. In the afternoon, there was a chill and the temperature rose to 105.8° F.; leucocytes, 4640.

Oct. 21. The temperature fell gradually to 98° F. at noon.

Oct. 22. There was a sharp rise in temperature with a chill at about 6 p. m., the temperature reaching 106.7° F. This was followed by a rapid fall, and, on Oct. 23, the temperature was normal.

On Oct. 24, the temperature rose slightly in the early morning hours, a sharp paroxysm beginning at 8, with a chill at noon, during which the temperature rose to 105° F. During all these days, the blood was carefully and repeatedly examined in both fresh and stained specimens. Neither parasites nor pigment was to be found and the leucocytes diminished to between 3,000 and 4000 per cmm.

At 8 p. m., on the 24th, quinine sulphate gr. x (0.65 gm.) every four hours was ordered.

On the 25th, the temperature was normal.

Early in the morning of the 26th, there was a slight paroxysm, much less intense than the preceding but lasting a full 24 hours. After this, the temperature remained permanently normal. Quinine was continued for a long period of time and there was no relapse. Repeated examinations of blood showed no parasites whatever and no pigment.

Now, the history of this case, the time of the year at which it occurred, the character of the febrile curve, the palpable spleen, the leucopenia and the apparently specific action of quinine, leave no serious doubt in one's mind that this was a case of malaria, probably æstivo-autumnal.

This is the first case in the history of the hospital in which we have been obliged to resort to the therapeutic test for the proof of the existence of a malarial infection.

Splenic puncture would probably have assisted us materially in the diagnosis. This was not performed because of the danger, minimal though it be. I have, myself, aspirated many spleens without the slightest trouble, and, in any case of emergency, I should have no hesitation in so doing again. Some years ago, however, I witnessed a fatal result of splenic puncture. The patient was a foreigner, unable to understand English. He failed to comprehend the procedure and jumped on the introduction of the hypodermic needle. This resulted in a small tear of the splenic capsule with fatal hæmorrhage into the peritoneal cavity. Although I feel convinced that with proper precaution, the danger is almost *nil*—and this has been the experience among more careful Italian observers, one of whom Prof. Bastianelli, is with us this evening, yet I cannot feel that splenic puncture is justified excepting in cases of real necessity.

It is interesting that Ruge * makes the surprising statement that "the mortality from splenic puncture, which has been observed up to the present time, amounts to 1½ per cent."

It is highly probable that the early administration of quinine was in this case responsible firstly, for the development of the regular paroxysms; secondly, for the disappearance of parasites in the peripheral circulation.

CASE IV.—*Grave Æstivo-Autumnal Tertian Fever. Remarkable Paucity of Parasites in the Peripheral Circulation. Convulsions and Death Following the Subcutaneous Injection of Quinine.*—In addition to these three cases, I would speak of another patient whose history is remarkable from various standpoints. The chart, as you will see, shows that which on first appearance appears to be a wholly irregular remittent fever. There are, however, certain very sharp remissions while many of the smaller oscillations are dependent upon the administration of baths. A careful study of the chart shows that every other day (on the 14th, 16th, 18th and 20th of October) there was a sharp rise of temperature somewhere between 6 and 10 a. m. This is followed by a remission during the afternoon and night and a second rise on the following day with a fall occurring in the afternoon or evening. In other words, the chart suggests the pseudo-crisis and subsequent elevation first described in æstivo-autumnal tertian fever by the Italian observers. Such a chart might well suggest an æstivo-autumnal tertian.

This patient was a sailor on a bay boat, a Spaniard, aged 29, who was said to have had malaria 13 years before. One week before entry, he began to complain of abdominal pain and diarrhœa. Four days before entry, there was headache, anorexia and nausea.

On Oct. 12, 1909, he was admitted at about 2 p. m. with a temperature of 105.8° F.; pulse, 104; respiration, 24. His appearance was typhoidal; the spleen was large, soft and palpable; there were several suggestive rose spots. The blood showed no parasites. The count was:

R. B. C.	5,280,000
W. B. C.	5,600
Hæmoglobin	90%

The coagulation time was three minutes, thirty seconds.

Urine: Normal color; sp. gr., 1.015, slight trace of albumen. In other respects, not remarkable.

On Oct. 13, 1909, I saw the patient on a morning visit. The temperature had fallen from nearly 106° to 99.4° F. He had a characteristically typhoidal appearance. The temperature was regarded as suggestive of malaria, but fresh and stained specimens of blood were negative. The Widal test was negative; the Diazo reaction was positive.

The chart illustrates the course of events. Daily blood examinations revealed no parasites. There was a leucopenia of 3,800 to 5,200. Five days later, a slight jaundiced tint was noted. The blood pressure, which at the outset ranged from 97-114, was on the 19th, 84 mm. Hg.

I next saw the patient on Oct. 20, 1909, just a week after my first visit. At that time, the temperature was about 105° F. There was a great change in the general picture. The facies was very dull and typhoidal. There was a very distinct anæmia and a slight greenish-yellow jaundice. The respirations were from 28 to 30. The liver was readily palpable. The appearance was wholly characteristic of malaria. A fresh specimen of blood was taken immediately and a considerable number of æstivo-autumnal parasites were found. These were for the most part bodies containing

* Einführung in das Studium der Malariakrankheiten, 2 aufl. 8°, Jena, 1906, Fischer, 221.

a few fine pigment granules, often arranged as a central mass, sometimes in a block (pre-segmenting bodies). The patient was obviously an ill man. It was suggested that he be given vigorous treatment, i. e., quinine bi-muriate gr. xv (1 gm.) in 10 cc. normal salt solution intravenously, to be repeated, if necessary, in four hours, and afterwards, quinine sulphate gr. v (0.325 gm.) every four hours by mouth.

The solution was not made by the apothecary until several hours after the visit and then, by a misunderstanding, of double strength, so that at 12 o'clock on the 20th, the patient was given quinine bi-muriate gr. xv (1 gm.) in 5 cc. of normal salt solution. Immediately after its introduction, there was a momentary convulsion accompanied by a slight twitching of the eyelids and lower lip, followed at once by general spasmodic contractions of the trunk and extremities. The eyes were rolled up and the head was somewhat retracted and turned to the right. Recovery was almost instantaneous and the patient soon seemed better than he was before. Thereafter, he was given quinine sulphate gr. x (0.6 gm.) by the mouth, every four hours.

Oct. 21. At 1 a. m. the patient was given a second intravenous injection of quinine bi-muriate gr. xv (1 gm.) without unpleasant results. In the morning, the temperature had fallen to 100° F., the pulse was from 90 to 100, and the patient seemed better. At 4 p. m., however, the temperature was rising again and a third intravenous injection of quinine bi-muriate gr. xv (1. gm.) was administered. Immediately upon its introduction the patient began to show convulsive twitching of the eyelids and lips; this was followed by a general convulsion. There was marked cyonosis; the pulse disappeared; the patient failed to respond to stimulants or artificial respiration.

Re-examination of the stained specimen of blood made on the 19th, showed, after long search, two characteristic æstivo-autumnal rings, which had been overlooked on a previous examination.

The *necropsy* made by Dr. Thomas twenty-eight hours after death, showed a severe but not intense malarial infection. The brain showed nothing remarkable—little pigment in the vessels. The spleen was large and soft, and microscopically showed much pigment—for the most part in leucocytes. Smears showed numerous segmenting parasites. The liver weighed 2700 grammes and was of a slate color; the cut surface was opaque. There was marked parenchymatous degeneration and the capillaries contained much pigment. The bone marrow showed numerous parasites in smears.

Both kidneys showed marked cystic degeneration,—the right measuring 16 x 10 x 7 cm. The entire surface was studded with cysts, the diameter of which ranged from a millimetre or less to 2½cm. The contents varied in color—clear—brownish—opalescent, and in some instances apparently contained changed blood. The pelves were greatly dilated. On section, the tissue which remained showed few changes in gross, but microscopically, there was a definite increase in fibrous tissue and some congestion of the vasa recta; in the portion of the kidney showing cystic change, there was considerable cloudy swelling with marked increase in fibrous tissue. The cysts were lined with cuboidal epithelium.

This case is exceedingly interesting as an example of grave infection with few parasites in the peripheral circulation throughout a week of study and observation.

The occasional absence of parasites in the peripheral circulation, especially in grave cerebral cases, has been emphasized by many observers, notably by Bastianelli. I have never seen, however, a case of such severity with so long an absence of parasites.*

The correct diagnosis was suggested here by the character of the fever, the general appearance of the patient and the leucopenia, and, even in the absence of parasites, I should have ordered quinine when I saw him on the 20th.

The most interesting point in connection with the case is the question as to the cause of death. From the result of the necropsy and from my observation of the patient, I should feel sure that it was *not* due directly to his malarial infection; on the other hand, I should feel reasonably sure from the history of the case that it *was* directly due to the intravenous injection of the quinine.

The literature upon quinine poisoning is very large and there are many instances of apparent death from large doses. The amount administered to this patient was, however, by no means remarkable, although considerably larger than that which is customary in this hospital. Several points are, however, worthy of note.

The first of these is the concentration of the dose. The speaker has always been in the habit of giving quinine intravenously according to the method of Bacelli in a solution consisting of

	gm.
Quin. dihychlor.	1.
Aquæ	10.
Sod. chloridi	0.065,

one-half of this being given in one median basilic vein and one-half in the other. In this instance, a dose of double the concentration was given at once. The patient had received 6 grammes of quinine in 24 hours, 7 in 28 hours, 3 grammes having been administered intravenously. The direct sequence of the symptoms in connection with the first and third injections of quinine was such as to leave little doubt as to the relation of the dose to the manifestations. While the dose was certainly strikingly concentrated, yet one must probably assume also that the individual was hyper-susceptible to the drug.

The specimen of quinine was from the same sample which had been used in other cases, and, so far as could be made out, showed no impurity.

A point of interest in connection with the case which may have an important bearing upon the fatal outcome, is the fact that the patient had cystic disease of his kidneys. Prof. Abel was much impressed by this fact, feeling that it suggested strongly that an unusual retention of the drug might have contributed toward rendering the patient more susceptible to the last dose. It must be said that the excretory powers of the kidneys seemed to be good and that anatomically, there was still considerable cortical substance. However this may be, the observation seems to be worth recording. I have for years been in the habit of advising the intravenous injection of quinine in urgent cases. Such an experience as this would certainly suggest caution in administering a solution of a concentration greater than 10 per cent. More than this, it points, it seems to me, to the advisability of conservatism in the administration of quinine intravenously in other than urgent cases of pernicious malaria.

In conclusion, let me emphasize one point, an old lesson, after all, which these two latter cases illustrate, i. e., that while careful and repeated examinations of blood in a vast majority of cases answer the question as to the presence or absence of malarial infection, really grave malaria may exist for considerable periods of time without demonstrable parasites or pigment in the peripheral circulation. In case of doubt, do not delay too long before applying the therapeutic test.

* Although I did not examine these daily specimens, seeing the patient but twice, yet I am sure of the care with which the case was followed by a most capable ward physician.

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THE PREPARATION OF ANTITOXIN.*

By E. J. Banzhaf, Ph. D.,

(Research Laboratory, New York City Board of Health.)

I accepted the invitation of your secretary, Dr. Moss, to speak to this well-known medical society, of the Johns Hopkins Hospital, upon the subject of antitoxin, with a mixed feeling of pleasure and trepidation. With pleasure at the honor bestowed upon me, through your secretary, and with trepidation that I might not fulfill your expectations. Inasmuch as the protective and curative value of the antitoxins is well established, the chemistry of these antibodies is possibly not so attractive as researches on the more baffling diseases. However, any knowledge we can gain from the chemistry of the antibodies will help to solve other difficulties in general biology, physiology and pathology.

It is now about fifteen years since diphtheria antitoxin was introduced for the treatment of diphtheria. Hopes were entertained that the antitoxin would be isolated and purified. Up to the present time these hopes have been only partly fulfilled.

As early as 1893, Brieger and Ehrlich attempted to isolate the antitoxin from the milk of immune animals. Smirnow, in 1895, was probably the first to work with antitoxic horse serum. He showed that the active substance was precipitated with the globulins on saturating the serum with magnesium sulphate.

Brieger and Boer, in 1896, precipitated the globulins by adding neutral salts of the heavy metals and found the antitoxin in that protein. Aronson, in 1897, stated that the globulin precipitated by dialysis contained antitoxin.

Dieudonné showed that the globulins precipitated by carbon dioxide did not contain antitoxin.

The protein precipitate, obtained by both these workers, corresponded to the globulins of the serum as originally defined. This globulin is now known as euglobulin. Brodi, in 1897, separated the globulins into four fractions, by the progressive addition of ammonium sulphate to one half saturation. All four fractions contained, however, relatively equal amounts of antitoxin. Belfanti and Carbona, Freund and Sternburg, Marcus, Seng, Hiss, Atkinson and others confirmed the results of Brodi and Dieudonné.

Atkinson, in 1900, working in the Research Laboratory, saturated with sodium chloride a solution of globulins containing the antitoxin. By employing heat, he differentiated the globulins into several fractions containing antitoxin. The antitoxin corresponded to the quantities of globulin in the precipitates.

Pick, in 1901, attempted to differentiate the active portion of the serum by fractional precipitation with ammonium sulphate.

Pröscher attempted to isolate and establish the non-protein nature of antitoxin by digesting the serum with trypsin. He stated that in this way he obtained a solution containing antitoxin which was free from protein.

Mellanby and I, working independently in 1908, could not confirm Pröcher's work. The ratio of digestion of the protein was approximately the rate at which the antitoxin was destroyed.

That the antitoxins belong to that class of substances known as proteins, practically all investigators now agree.

It might be well, at this point, to call your attention to the fact that, in the early days, the antitoxic serum contained less than 100 units per cubic centimeter. This low grade of serum was principally due to the inability to produce a strong diphtheria toxin. Park and Williams, in 1896, isolated a diphtheria culture from a child with a mild case of diphtheria. This culture proved to be a strong toxin producer and is now used and known throughout the world as "Culture No. 8." With the toxin from this culture a more potent antitoxin was gradually obtained. Thus smaller injections of serum were required to give the same number of units. This was desirable, for it was early recognized, by Pirquet and Schick, that injections of antitoxic sera were sometimes followed, after an incubation period of eight to thirteen days, by urticarial eruptions, joint pains, fever, swelling of the lymph nodes, edema and albuminuria. These disturbances have no direct bearing on the antitoxic properties of the serum, for they showed that normal horse serum produces the same effects. This reaction Pirquet and Schick have termed "Serum Sickness."

Although almost all the investigators mentioned, and others, established the fact that the antitoxins were associated with the globulins, there was practically no record of actual administration of these globulins. Park, in 1900, first studied the possibility of eliminating serum rashes and other disturbances, by testing a considerable number of cases with an antitoxic globulin prepared by Atkinson. The results were practically identical with an equal number of cases treated with the whole serum from the same horse.

In 1905, Gibson, working in the Research Laboratory, perfected a practical method of recovering the pseudoglobulin containing the antitoxin. He placed the precipitated globulins obtained by half saturating with ammonium sulphate, in saturated sodium chloride solution. In this way the globulin, insoluble in saturated sodium chloride solution, *i. e.*, euglobulin, present in Atkinson's preparation, was eliminated. The pseudoglobulin, which is insoluble in the saturated sodium chloride, was precipitated with acetic acid. This precipitate was then dialyzed. The finished concentrated product was about two and a half times the original potency.

With this product, Dr. Park again took up the study of rashes. The results of this work were favorable. Less early

* Read before the Johns Hopkins Medical Society, December 19, 1910.

rashes, and constitutional disturbances, were noted. This preparation was so satisfactory, that the New York Board of Health laboratory in 1906 sent out only this product. Other laboratories then followed suit.

At Dr. Park's suggestion, Gibson and I fractioned the antitoxic serum with progressive amounts of ammonium sulphate up to one-half saturation. Our experiments resulted somewhat differently from those reported by Brodi, Atkinson and Pick. We found that the pseudoglobulin of the higher fractions contained uniformly much more antitoxin, per gram protein, than that precipitated by lower concentrations of ammonium sulphate.

Both from a theoretical and practical view, the results were very satisfactory. This fractioning of the antitoxic sera was adopted in preference to Gibson's original method.

After the partially purified antitoxin product was well established, the question occasionally arose regarding its protective and curative value in comparison with that of the whole serum from which it was derived. According to certain French investigators and others, the antitoxic serum most active therapeutically is not always the one which contains the greatest number of antitoxic units. They maintain that the serum contains, besides antitoxin, other important protective and curative substances, which are not measured by the present method of standardization. For instance, they state that a given quantity of a 200-unit serum is occasionally more active, both preventively and curatively, than the same quantity of a 500-unit serum. Roux, Marfan, Martin, Momont, Cruveilhier, and lately Kraus and Schwoner, support the French views, while on the other hand, some of the German, English and American investigators support Ehrlich's method of standardization.

The conclusions of the work of Steinhardt and myself, in which we used several strains of a 24-hour agar culture of live diphtheria bacilli, with antitoxic serum of widely varying strengths, were that, with diphtheria in the guinea-pig, the therapeutic value of the serum depended upon the number of antitoxic units present. No other substance, besides the antitoxin, played an important rôle. The conclusions of our work on the concentrated globulin containing the antitoxin, and the whole serum from which it was derived, were the same as just given. Since our work, in 1908, Kraus and Schwoner have published four papers on this subject. The conclusions of all of these are diametrically opposed to our findings. Berghaus, working in Ehrlich's laboratory, corroborated our findings, and stated that he found great discrepancies in Kraus' standardization of the antitoxic value of the serum.

I might state that we obtained three different samples of the horse serum that Kraus and Schwoner used in their work. These were labelled to contain 200, 350 and 600 units, respectively.

In my standardizations, I found the first to contain 185 units. Deterioration in transit might account for this difference. The sample said to contain 350 units actually contained 465 units. The 600-unit sample contained only 360 units. In regard to the accuracy of their standardization on the two latter samples, no comment is necessary.

We will now discuss briefly the work by Gibson and myself, on the quantitative changes in the proteins in serum of horses in the course of immunization.

Seng, Joachim, Atkinson and Ledingham observed that when an animal is immunized against bacterial toxins, there result certain characteristic quantitative changes in the proteins of the blood plasma. The content of the globulins is strikingly increased even up to double the normal amount; at the same time, there is a diminution in the albumin.

Atkinson showed that this globulin increase is in some degree proportional to the antitoxic potency of the serum.

Ledingham, in a paper published while our work was under way, gave results of the determination of the total protein, the globulins and the albumin in the course of immunization against diphtheria toxin. The serum was obtained at short intervals from two horses.

In one horse, which failed to yield a high grade of antitoxin, the globulins of the serum were not essentially increased over the normal. The other horse gave ultimately a 650-unit serum; the globulins here had progressively increased along with the antitoxic potency. From Ledingham's results from the two horses, a relation between the development of the antitoxic properties and the increase in the globulins is indicated. Ledingham and Joachim state that the increase of the globulins is in the euglobulin fraction.

It may be desirable to discuss the fractioning of the globulins. The globulins are commonly stated to consist of at least two different proteins, the euglobulin, and a more soluble protein, the pseudoglobulin. The euglobulin is insoluble in pure water, and accordingly precipitated on dilution or dialysis; it is also thrown down by slight acidification. The pseudoglobulin belongs by definition to the group of true albumins; *i. e.*, it is soluble in pure water. In practice, investigators have commonly used the fractional precipitation by salting out with ammonium sulphate. A half volume of saturated ammonium sulphate solution is added to the serum; *i. e.*, one-third saturation. The precipitate is the euglobulin. The separation is not sharp at all. The filtrate contains the albumin and pseudoglobulin; the latter can be thrown down by the further addition of saturated ammonium sulphate solution to half saturation. In current writings the identity of this "fractioned" euglobulin has been confused with the slight precipitate obtained on dialysis, dilution, or slight acidification, in spite of the early work of Freund and Joachim. By employing the ammonium sulphate fractioning, Ledingham, like Joachim, found the increase in the globulins affected the euglobulin more than the pseudoglobulin fraction, *i. e.*, the great increase in the globulins took place in the non-antitoxic protein. Ledingham's interpretation of his results, as regards this point, seems inconclusive, for he does not grasp the significance of the limitations in the salt fractioning of the proteins. His observations, associating the increase in the globulins with the questionable euglobulin fraction, were made by direct precipitation of the serum with half its volume of satu-

rated ammonium sulphate solution; *i. e.*, one-third saturation. When re-precipitated for purification, the protein was usually re-dissolved to the original volume and the same amount of ammonium sulphate solution added as before. Inasmuch as the globulins may have been doubled as the result of immunization, would not a great part of this increase be found naturally in the euglobulin fraction, since solubility of the protein must be considered? The precipitate obtained at one-third saturation is not free from antitoxin. It may contain the greater part of it when the undiluted serum is precipitated by the addition of a half volume of saturated ammonium sulphate solution. To illustrate this, Gibson and I precipitated ten cubic centimeters of plasma by the direct addition of five cubic centimeters of saturated ammonium sulphate solution; again, ten cubic centimeters of the plasma were diluted to $33\frac{1}{3}$ cubic centimeters with water and precipitated by the addition of $16\frac{2}{3}$ cubic centimeters of the saturated ammonium sulphate solution, and finally, a third ten cubic centimeters of the plasma were diluted to $66\frac{2}{3}$ cubic centimeters with water and precipitated with $33\frac{1}{3}$ cubic centimeters of the saturated ammonium sulphate solution. We then had ultimate dilutions of 15, 50 and 100 cubic centimeters each, at one-third saturation. The precipitates were allowed to stand for a few hours, with occasional shaking, to permit mechanically precipitated protein to return into solution. The precipitates, at the three dilutions, were then determined. We found the fraction to include 5.39, 1.78 and 0.98 grams of protein per 100 cubic centimeters at the three respective dilutions.

Because of this unsatisfactory characterization of the "eu-" and "pseudo-" globulin by the ammonium sulphate fractioning, it seemed of interest to differentiate in some modified way the relative globulin changes. We have accordingly determined as euglobulin that part of the globulins precipitated on saturating with sodium chloride.

Freund and Joachim state that saturation with sodium chloride precipitates all the euglobulin, but that this includes only a part of the product obtained at one-third saturation ammonium sulphate. We may consider that we have as sharp a differentiation as possible between the two globulins. The sodium chloride separation, probably, more truly represents the common conception of the euglobulin and pseudoglobulin, though the ammonium sulphate fractioning, heretofore, has usually been employed. With your permission, then, we shall term the globulin soluble in saturated sodium chloride solution, pseudoglobulin; and the globulin insoluble in saturated sodium chloride solution, euglobulin.

The observations of Atkinson and Ledingham were the only determinations of a quantitative relation of the globulins and the antitoxic potency throughout the course of immunization.

The subject is of extreme importance when the significance of the problem as to the chemical nature of the protective substances is considered, because of the constant relation of these substances with the pseudoglobulin, *i. e.*, the globulin soluble in saturated sodium chloride solution. In our work we followed quantitatively the protein changes in the plasma of eleven horses. The characteristic globulin increase during immunization was observed in all the horses. The increase was found in the pseudoglobulin.

We allowed about six weeks to elapse after the immunization was started, before taking a sample bleeding for analysis. From this time on samples were taken every week during the treatment. This first estimation gave us in all the horses an increase in the pseudoglobulin varying from 45 to 120 per cent, and a loss of albumin from 25 to 85 per cent. Thus it can be seen that great protein changes had taken place after only six weeks immunization. That we missed the time of early changes we realized after it was too late.

The total proteins showed an increase of from 20 to 45 per cent. This increase was at its highest after about two months of treatment and was true in all the horses regardless of unit content. After two and a half to three months treatment the total proteins decreased and fluctuated somewhat throughout their entire immunization.

The proteins, however, never dropped to the normal amount even though weekly full bleedings were taken; in some cases extending over a period of many months. This, therefore, shows us that the influence of repeated bleedings does not essentially influence the protein changes induced by immunization. These remarkable regenerative processes are worthy of note.

The highest antitoxic value obtained from these horses was 850 units; at this time the albumin was 75 per cent lower than this horse's normal amount, and the pseudoglobulin 90 per cent higher. An exceptionally refractory horse, with its highest value 125 units, showed a decrease of 55 per cent albumin, and an increase of 85 per cent of pseudoglobulin. Thus it can be seen that the decrease of albumin and the increase of pseudoglobulin take place in an immunized horse regardless of the antitoxic content. We wish to state, however, that the maximum antitoxic potency does not necessarily mean that other immune substances are present in greatest amounts or that they are developed in corresponding degree with the antitoxin. Immunization aimed to be of specific character may lead to the production of other antibodies. Collins and others have shown that group and specific bacterial agglutinins can be developed by immunizations against yeasts, enzyme preparations and nucleins.

These experiments afford actual proof of the development of many widely different anti-substances during immunization. A similar stimulation, leading to the formation of numerous antibodies besides the precipitins and specific antitoxins, probably occurs on immunization with bacterial toxins. Such substances may represent the increase in the pseudoglobulin with which they are associated.

In the course of immunization, then, there is a marked increase (even over 100 per cent) in the pseudoglobulin content of the blood plasma. This increase tends to precede the development of maximum antitoxic potency and is quantitatively independent of the latter. With a diminution of the potency, the pseudoglobulin increase is reduced, with a tendency for this change to precede the antitoxin variation.

This work on the protein changes brought out the fact that the proteins eliminated in the process of purification were much less than we had expected. For, as is well known, in the average normal horse serum the proteins are distributed as follows: albumin 40 per cent; pseudoglobulin 12 per cent; euglobulin 18 per cent. Thus it would appear that about 58 per cent of the protein was eliminated in the purifying process. We now know, however, that in the average immunized horse the proteins of the serum are distributed as follows: albumin 12 per cent; pseudoglobulin, containing the antitoxin, 78 per cent; euglobulin 10 per cent.

Thus only 15 to 25 per cent of the protein could be eliminated, depending on the fluctuation of albumin and euglobulin content of immunized horses.

Early in the spring of 1908, an observation of Stark's came to my notice.

Stark showed that when egg albumen was heated for one hour at 56° C. a portion of it was converted into a body, which appeared to be a globulin because of its precipitation and solution reactions. This fact aroused my curiosity as to what result would be obtained if antitoxic serum or the antitoxic pseudoglobulin solution was heated. With this in view, I carried out a large series of heating experiments with results that were rather gratifying as a means of further purifying the antitoxin. This gave at least 50 per cent purer antitoxin than had ever before been obtained. In order to make this clear, we will take the serum of an immunized horse. The proteins of this animal's serum, we will assume, are distributed as follows: albumin 12 per cent; pseudoglobulin, containing the antitoxin, 78 per cent; euglobulin 10 per cent. If we heat this serum from twelve to fifteen hours at a temperature of 57° C. we will have a rearrangement of the precipitation characterization of the proteins. If we now estimate the albumin, we will find, instead of 12 per cent, only about 9 per cent; the pseudoglobulin, containing the antitoxin, instead of 78 per cent, only about 50 per cent; and the euglobulin, instead of 10 per cent, will be increased to about 41 per cent. All of the antitoxin, with the exception of about 2 per cent which is lost by the heat employed, will be found in the remaining pseudoglobulin.

From a scientific standpoint, this is extremely interesting, in that it opens a new field for further investigation, which may throw more light on the chemical characteristics and the nature of antitoxin.

Formerly, all the evidence was in favor of the pseudoglobulin nature of the antitoxins. The antitoxins had every known character of this protein. Mellanby, in 1908, stated that antitoxin is actually a part of the pseudoglobulin. Now, however, we know that we can heat the pseudoglobulin, containing the antitoxin, and actually change the precipitation limits of about one-third of it, *i. e.*, from the pseudoglobulin to the euglobulin condition, without loss of antitoxin. From this we can conclude that the pseudoglobulin in an immunized horse is not necessarily antitoxin. The chemical combination of pseudoglobulin and antitoxin, if such is the case, is not a fast and stable one. If a union does exist it must be merely an unstable combination that can be disassociated by heat. As an analogy to this, Calmette's work on cobra venom and its antitoxin might be mentioned. Calmette, you will remember, showed that when neutral mixtures of venom and antitoxin were heated, the antitoxin lost its identity and the venom regained its toxicity. He stated that the mixture of venom and antitoxin form an unstable combination and that each of the two substances preserves its individuality in the mixture.

From the knowledge we now have in regard to antitoxin, it is justifiable to conclude that there is a union between the antitoxin and pseudoglobulin, either a mere adsorption or an unstable chemical combination, and that the antitoxin can be disassociated from the pseudoglobulin without losing its identity.

THE CLINICAL VALUE OF THE DETERMINATION OF THE CATALYTIC ACTIVITY OF THE BLOOD.

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Catalase is an enzyme of universal occurrence characterized by its power of decomposing hydrogen peroxide with the liberation of water and molecular oxygen. Further than this very little is known concerning its function. Its intimate occurrence with peroxidase, however, has led to the assumption that these two ferments are associated in the oxidative phenomena of the body.

The following report is based upon a series of experimental and clinical investigations in which C. R. Meloy, G. R. Henry, F. McPhedran, J. P. Pratt, and W. B. Rogers were associated with the author.

EXPERIMENTAL WORK.

The study of the catalytic activity of both normal and diseased human tissues and of the blood in experimentally produced diseases in animals is confined to a few isolated observations. For this reason we have first interested ourselves in this field and the results of these investigations seem so essential for the proper interpretation of the clinical application of the test that they will be briefly summarized.

The determination of the catalytic activity of human tissues led to the conclusion that all of the tissues of the body were reduced in their power to split hydrogen peroxide in chronic

nephritis, and that this reduction varied directly with the severity of the condition. The lowest activity was obtained in uræmia. In no other disease, including eclampsia, was this universal decrease in the activity of the enzyme found (1).

After it had been determined that the catalytic activity of a single rabbit's blood is constant from day to day over long periods of time the influence of the kidney and its function upon the catalase of the blood was studied with the following results: after ligation of the ureters, bilateral nephrectomy or uræmia, resulting from uranium nitrate nephritis there is a fall in the catalytic activity of the blood which becomes more and more evident as death is approached. The tissues of such animals at autopsy show a like reduction (2).

The effect of salts on the catalytic activity of the blood of living rabbits was then investigated for the following reasons, (1) because it is well known that the addition of various salts to a catalase extract in vitro influences the action of the enzyme, and (2) because the decreased activity of the catalase of the blood in nephritis might in some way be related to the salt retention in this disease. The results seem conclusive. Acids, alkalies and salts all reduced the activity when injected intravenously. In these experiments it is important to make observations during the injection and at short intervals after the injection has been discontinued, since there is a rapid compensation on the part of the organism with a return to normal of the catalytic activity of the blood. For example, 20 cc. of 5 per cent bicarbonate of soda solution causes a marked fall in the activity of the blood which is rapidly recovered from (1 to 5 minutes after the injection has been discontinued) and then a much more marked fall in the activity followed by a much longer time for compensation occurs after 6 cc. of the same salt. This continues on further injections until compensation is lost and death ensues. It is possible on this basis to construct a hypothetical explanation for the decline of the catalase in nephritis and uræmia (3).

Further studies on the relation of various organs to the catalytic activity of the blood were made with these results. After the extirpation of many organs there is a transient fall in the catalytic activity of the blood. The fall is permanent after extirpation of the thyroid, but is compensated if thyroid be fed (4).

During the above experiments it was found that following an acute peritonitis there may be a sharp rise in the catalytic activity of the blood. This rise usually occurs within 6 hours after the peritonitis is produced, and may continue for several days. The curve of activity is entirely independent of that of the body temperature or white blood count, but corresponds to an increased number of erythrocytes (5 and 6).

From the above experiments several factors influencing the catalytic activity of the blood can be deduced, namely the number of red blood cells, the function of the thyroid and kidney, and the action of salts, acids, and alkalies.

Clinical Application of the Test (7).

Method.—.025 cc. of blood is removed from the lobe of the ear in a pipette. This is diluted in 10 cc. of water; 5 cc. of this dilution suffices for a test. It is placed in a 100 cc. bottle in which there is also a vial with 5 cc. of neutral hydrogen peroxide. The large bottle is connected with a gas burette and then uniformly agitated in order to bring the blood and hydrogen peroxide in contact. The amount of oxygen liberated is measured over a given period of time (15 seconds). The procedure requires only a few minutes, the error is slight and no precautions beyond ordinary room temperature and clean apparatus are necessary.

A series of 100 normal individuals of different age and sex were first studied; 80 per cent of these vary within physiological limits, i. e., 5 cc. of a 1-400 dilution of their blood will liberate from 13 to 17 cc. of oxygen from 5 cc. of neutralized 3 per cent hydrogen peroxide in 15 seconds. In the other 20 per cent the amount of oxygen liberated varies within wide limits, 12-22 cc. These variations are independent of the number of red blood cells and hemoglobin percentage. The explanation of this variation is at present not forthcoming. It is, however, of the utmost importance to bear it in mind when interpreting the activity of the blood in diseased conditions.

On the other hand the catalytic activity of the blood of a single normal individual is constant from day to day over long periods of time and in this way a base line can be obtained from which the significance of any change in the activity can be readily interpreted.

The Catalytic Activity of the Blood in Disease.

Typhoid Fever.—Fifteen cases were followed throughout their illness with the following results. During the early days of their illness there was no change in the catalytic activity of the blood, but towards the third week there was a gradual fall accompanying the anemia. During convalescence the activity became normal together with the red blood count.

Diseases of the Respiratory Tract including lobar pneumonia, tuberculosis, and empyema (12 cases). There is a slight decline in the catalytic activity of the blood during the course of lobar pneumonia. The relation of this decline to the crisis and the salt metabolism of this disease has not yet been determined. In other diseases of the respiratory tract there is no noteworthy variation in the power of the blood to split hydrogen peroxide except where the disease is accompanied by a severe anemia.

Acute Peritonitis.—In 4 out of 5 cases of acute peritonitis examined there was a characteristic rise in the catalytic activity of the blood. In one a reading had been made before the peritonitis occurred while in the other three the increased activity was confirmed by the decline to normal, following operation. In the one instance where no rise was obtained the reading was only made 20 hours after operation. In two cases of suspected peritonitis with high fever and leucocytosis the catalytic activity of the blood was normal, and in these cases the peritoneum was found clean at operation.

Diabetes Mellitus and Catarrhal Jaundice exert no influence upon the catalytic activity of the blood.

Diseases of the Thyroid Gland.—Four cases. In diseases of the thyroid gland both hypo- and hyperthyreosis, the catalytic activity of a single patient's blood is not constant from day to day. In hyperthyreosis the activity tends to increase while in hypothyreosis the activity assumes a level lower than normal. This may be of significance in interpreting the condition of the thyroid gland where the signs and symptoms are atypical.

Renal, Cardiac and Cardio-Renal Cases.—Twenty-four cases.

1. Despite the presence of a marked nephritis provided there are no symptoms of renal insufficiency (uræmia) there will be no marked change in the catalytic activity of the blood.

2. Where there is a chronic nephritis accompanied by indefinite symptoms of renal insufficiency the catalytic activity of the blood will be irregular from day to day and will tend to assume a level lower than normal.

3. In acute mercurial nephritis there is a fall in the catalytic activity of the blood.

4. With uræmic coma there is a marked fall in the catalytic activity of the blood which is permanent if the coma ends fatally but which recovers should the coma disappear.

5. With retention of urine due to obstruction of the lower urinary tract there is a marked decline in the catalytic activity of the blood. This decline may persist for some time but should the obstruction be removed the catalase will again rise.

Cardiac Cases.—Even in severe cardiac disease there is no significant change in the catalytic activity of the blood. In some cases it is high. This may be normal for these individuals as it will be remembered some normal individuals have a high activity. In no single case was the activity sufficiently decreased after many readings had been made to suggest renal insufficiency.

Cardio-renal Cases.—In three cases of cardio-renal disease where the clinical findings suggested a renal insufficiency the catalytic activity of the blood was normal. At autopsy only a chronic passive congestion of the kidneys, the result of a decompensated heart, was found.

Cerebral Hemorrhage.—In two cases of cerebral hemorrhage the catalytic activity of the blood was high. Whether this is an increase over normal is not known but it is clear that the high reading would differentiate apoplectic coma from uræmic coma.

THE CATALYTIC ACTIVITY OF THE BLOOD IN PREGNANCY.

Neither pregnancy nor labor have any appreciable effect upon the catalytic activity of the blood. Ten cases.

The toxæmias of pregnancies accompanied by coma and convulsions can be differentiated into two groups by the determination of the catalytic activity of the blood.

1. Cases where there is no change in the catalytic activity. These will include eclampsia without renal involvement. Seven cases.

2. Cases with decreased catalytic activity; three cases. These will include:

a. Chronic nephritis where the excessive work thrown on the kidneys by the fœtus will bring about renal insufficiency.

b. Eclampsia, etc., with marked renal involvement. The significance of this differentiation in the prognosis for future pregnancies is clear. In the first group future pregnancy may be normal. In the second it will most likely be complicated by a toxæmia, the result of renal insufficiency.

MALIGNANT DISEASE AND DISEASES OF THE HÆMATOPOIETIC SYSTEM.

The results are still too meagre to be of value.

The interpretation of the clinical results is entirely dependent upon the experimental work, and in many places will probably be unsatisfactory. The number of cases is likewise too few to allow of anything but broad conclusions. It seems, however, that the work will be of value in the study of the oxidative phenomena of the blood, in further detail than is allowed from the enumeration of the red blood cells and the determination of their hemoglobin content.

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DISTOMA PULMONALE IN WISCONSIN.

By Henry Hanson, M. D.

(From the Pathological Laboratory of the Milwaukee County Hospital.)

The finding of lung flukes (Distoma Pulmonale, or Paragonimus Westermanii) is of such rare occurrence and great importance that it seems to me the case in question should be reported. Up to the present time there appear to be only three specific cases in which this parasite has been found in domestic animals in this country. One case has been reported for man, an imported case seen in Portland, Oregon. In the March (1908) number of the *Denver Medical Times* and *Utah Medical Journal*, E. W. Lazell reported a case of "Cysticercus cellulosæ and Distomum pulmonalis in Brain, with Exhibition of Specimens." This paper deals so briefly with the case, and the description of the parasites is so incomplete that one can hardly feel satisfied to class them with the group of parasites known as the Paragonimus Westermanii, and yet the paragonimus is the only fluke which is known to get into the brain.

Up to the present time the disease has been unknown in the State of Wisconsin. The only two other States previously known to have these parasites are Michigan (Ann Arbor) and Ohio (Columbus and Cincinnati). In Ann Arbor the fluke was found in the lung of a cat and was sent to Dr. H. B. Ward of the University of Nebraska, who identified the parasite and wrote the first report of the presence of this lung fluke in the United States. The parasites were later sent to Stiles of the Department of Zoology, Public Health and Marine Hospital Service, U. S., who confirmed Ward's diagnosis and pronounced them identical with the Paragonimus Westermanii. In the second case the lung fluke was found in a dog in Columbus, Ohio, by Kellicott, who also referred this specimen to Ward. In the third instance the lung fluke was found in hogs slaughtered at the abattoirs in Cincinnati, Ohio. These cases cited, together with the finding of the disease in a cat and also two of her kittens (kittens born in the village of Wauwatosa, Wisconsin), add further proof of the endemic theory of the infection. This means that we have a new parasite to deal with. The reason this parasite has not been discovered before is most likely due to the fact that it has not been looked for extensively. There is no doubt in my mind that there are cases of this disease in human beings which have been overlooked simply because an infection of this kind has not been known to exist.

This parasite, as is well known to those who have had occasion to look up its history, is a particularly unwelcome one. It is especially important that medical men should be on the lookout for possible cases of this infection, parasitic hæmoptysis, which are probably called incipient tuberculosis on account of the obscurity of the physical lung findings. The scattered distribution of the cases referred to would also indicate that the parasite is quite firmly established and that it is more common than is generally known. The first finding of the parasite dates back to 1893, the first report by Ward to 1894. Other reports have appeared at intervals, to which references will be given at the end of this paper.

The present paper is especially concerned with the finding of lung flukes in two autopsied cats in Wauwatosa, Wisconsin.

I am indebted to Mr. Edwin Hirsch, of Wauwatosa, Wis., for the opportunity of making this study, since it is through his interest in the case that the parasite was discovered. He first noticed that one of the cats owned by the family was coughing and in order to determine the cause of the cough he killed and dissected the cat. Later when a second cat began to show symptoms it was brought up to the laboratory of the Milwaukee County Hospital where the cat was chloroformed and autopsied.

History of Cat.*

Case I.—The first case of lung flukes to come under our observation was that of a female cat. Early in the spring of 1906 she with three other kittens was found under an old lumber pile. The other kittens were taken away, but this one was kept and grew up as a family pet. After she had become somewhat more than a year old, we noticed that she had a very peculiar cough. This was not clear and free, but rather close and choking. We at first thought little of the matter and permitted the cat to remain a pet. The cough gradually grew worse and the cat seemed to lose weight. As we did not deem it well to have a sick cat as a pet we concluded to dispose of her. During the Christmas holidays of 1908 the cat was chloroformed and autopsied. The lungs at their apices were of normal color, but at their bases colored nodular areas were to be seen. Upon cutting into one of these areas we were greatly surprised to find two parasites contained therein. Upon opening the other cysts, for now it was evident that these dark colored nodules were such, other pairs of parasites were found. In all there must have been 6 or 8 different cysts and each contained two parasites.

Case II.—The second case of lung parasites was also in a female cat. The cat, a kitten of the cat in the first case, was born on March 25, 1908. When but a few months old she also gave indications of a throat or lung trouble by a choking cough. This gradually became more marked and the cat grew thin. Finally she had several hemorrhages and then she was chloroformed, and autopsied on Easter Sunday, 1909, in the Pathological Laboratory of the Milwaukee County Hospital.

Anatomical Findings.—With the exception of the lungs the findings were negative.

Lung of Cat.—The upper lobe of the lung is of salmon red color, crepitates and shows no infiltration except in the lower part where a few areas of induration can be seen which somewhat resemble tuberculosis nodules. The nodules vary in size. In the lower lobe there are more of these areas, some of which are from 1 to 2 mm. or more in diameter. These have a semitranslucent appearance, and are of an opaque grayish-white color. Other areas in the lower part of the lower lobe are of a dull dirty brownish-gray with a yellowish-green tinge in the underlying tissues. Along the mediastinal portion there are more of these grayish, dull, semitranslucent areas. In the lower part of the

* History written by Edwin Hirsch, Wauwatosa, Wis.

lower lobe one sees a projecting nodule and a more voluminous appearance in the lung. On section one cuts into a definite cyst which contains two lanceolate bodies somewhat coffee-bean shaped, but the blunter head end differs from the narrower tail end and thus to some extent destroys the analogy of the coffee-bean. The fluke resembles the larva of the potato bug (dorsal surface). The flukes each have a rounded dorsal and a flattened ventral surface.†

The flukes in this case measured 11 mm. long by 4 to 4.5 mm. wide and in the fresh live condition about the same in the dorso-ventral diameter. On inspection one can see dark, blackish-blue areas which, as I have found on further study, are the internal organs such as uterus and intestines. One of the flukes was cut accidentally and as a result secreted a dark biliary, viscid-looking fluid substance. Color of flukes, a reddish-brown. On section of the lung one finds a more or less infiltrated appearance, with nodules of varying size. The cut surface in such areas has a yellowish appearance and smears from these areas reveal a large number of eggs with a chitinous yellow shell. The smears are obtained by simply drawing a slide across the fresh lung surface. These eggs are oval, one end blunter than the other, the blunter end has a definite operculum. Within the eggs are found varying pictures. Some seem to be simply an empty shell while others have a definite yolk or nuclear structure in the center of the egg mass. The eggs with the yolk mass also contain some cells which have the appearance of endothelial cells, but have a very granular protoplasm, almost resembling the granules of the *Herzfehlerzellen*.

Microscopic Findings.—Section, stained with hæmotoxylin and eosin, taken through the fibrous cyst with some of the surrounding lung tissue. In the gross this shows a fibrous capsule about the parasites, about 1 mm. thick with a dense surrounding infiltrated tissue. Microscopically this is found to be composed of whorls of fibrous tissue with some round, spindle and fibroblastic cellular infiltration. The picture is that of a chronic inflammation resembling a fibrous pneumonia. In the center of this cyst there are some organizing blood clots and an accumulation of round cells, other leucocytic cells, and here and there an occasional egg. Outside of this cyst wall one sees a dense pneumonic infiltration, of endothelial, round and polymorphonuclear cells, also giant cells. Within the eggs one finds in many instances a nuclear cleavage, probably the beginning development of the egg. Such a theory has already been advanced by one writer and discredited by others. Nevertheless such is the picture which is found in the eggs in the sections from this case. The section also shows empty shells of eggs. The significance of this cannot be definitely stated. The eggs of other flukes are not known to develop and liberate their ciliated embryos in the tissues.

Among other flukes which occur and may be pathogenic for man are the following: Liver flukes (Fasciola hepatica, Fasciola gigantica), and the Venal Distoma (Schistosoma hæmatobium), the latter is also known as Bilharzin, the disease, Bilharziosis or Egyptian Hæmaturia. The Schistosoma is a very rare parasite in this country and not more than six or seven cases have been reported. The last of these reports which I have seen is "Parasites Found in New York City, Archives of Internal Medicine, September 15, 1908, Vol. 2, No. 2, by H. S. Patterson." Other flukes have also been reported, e. g., Ward in 1895 reported "The European Cat Fluke, Opisthorchis felineus," from cats in Nebraska. This fluke, however, infests the gall ducts of the domesticated cat, and is not found in the lungs.

Clinical Diagnosis.—Diagnosis of lung fluke infection can be made by examining unstained specimens of sputum from suspected cases. The finding of large, yellowish, oval eggs should at once make the diagnosis. There are no other eggs the size and shape of the lung fluke eggs which are likely to be found in the sputum. "The eggs are always present and constitute the only constant specific character." Stiles (Osler's Modern Medicine) estimates that as many as 12,000 eggs may be expectorated in a single day. The cough is at first a hard, dry, chronic cough. The sputum is said to have a peculiar odor, probably due to the blood which it contains, and is of a rusty color.

"The lethality has not been determined but probably varies with the intensity of the infection." (Stiles, *l. c.*)

The lesson to be drawn from finding this parasite in this vicinity and other parts of the country is that there may be

†For a detailed description of the parasite I will quote from Illustrated Key to the Trematode Parasites of Man. Bulletin, No. 17, Hygienic Laboratory, Treasury Department, Washington, D. C.

"Type Species Paragonimus Westermanii (Kerbert, 1878).

"The Asiatic Lung Fluke—Paragonimus Westermanii—(Kerbert, 1878)—Stiles & Hassall—1900 of Man.

"*Specific Diagnosis.*—Paragonimus: 8 to 16 mm. long (after Kellicott 15 to 20 mm.), 4 to 8 mm. broad, 2 to 5 mm. thick; plump pinkish to reddish-brown (alive), slate color when preserved; live specimens are depressed and with a variable outline; preserved specimens often oval to elongate pyriform, transverse section round or nearly so, anterior end bluntly rounded, posterior end less blunt. Oral sucker 0.53 to nearly 0.75 mm. (Leukart) or more; 0.864 by 1.017 mm. or 1 to 1.4 mm. (Ward); or 0.40 to 1.12 by 0.83 mm. (Stiles and Hassall); 0.78 mm. (Kerbert) in diameter, terminal or subterminal in different specimens from the same lung. Ventral acetabulum 0.6 to at most 0.75 mm. (Leuckart); 0.78 mm. (Kerbert); 0.75 to 1.017 mm. (Ward); 0.88 to 1.2 by 0.86 to 1.44 mm. (Stiles and Hassall) very slightly larger than oral sucker. Skin provided with broad scale-like spines. Pharynx elongate; esophagus very short so that the bifurcation of the intestines is considerably anterior of the ventral acetabulum; intestinal ceaca usually somewhat zigzag some distance from each other run irregularly to posterior end. Genital pore, often indistinct, close to caudal margin of ventral acetabulum, may be in the median line or immediately to right or left of it. Male organs: Cirrus or cirrus pouch absent; ductus ejaculatorius is straight; testicles tubular, ramified, one slightly posterior of the other on each side of the median line. Female organs: Ovary branched lateral, right or left of medial line, somewhat posterior of acetabulum and anteroventral of transverse vitello-duct; on the opposite side of median line and at about the same height is situated a lobate shell gland and a rather short massed uterus: in some specimens the latter may spread across the median line and partially cover the ovary; folds of uterus extend ventrally of shell gland; vitellaria marginal, highly developed, extending anterior to posterior extremity, often leaving but a small portion of the dorsal and ventral median fold uncovered; transverse vitello-ducts dorsal; vitelline reservoir large; Laurer's canal present. Eggs oval, 80 to 100 μ long by 56 μ broad (Leuckart); 96 to 118 μ long by 48 to 53 μ broad (Ward); 68 to 96 long by 48 to 60 μ broad (Stiles and Hassall); yellow shell. Miracidium ciliated, develops after eggs leave host. Sporocyst, redia, cercaria, and intermediate host undetermined.

"*Habitat.*—Lungs and brain (occasionally in other parts of the body), royal tiger (Felis tigris), domesticated cat (Felis catus domesticata), domesticated dog (Canis familiaris), swine (Sus scrofa domesticata) and man (Homo sapiens).

"*Geographic Distribution.*—China, Japan, Formosa, occasional imported cases in Europe, some cases of endemic infection in the United States."

more of them in persons suffering from vague pulmonary symptoms, and that the physicians should always be on the lookout for them, especially where the parasite is now positively known to exist. All efforts should be made to determine, if possible, the mode of infection. So far the secondary host for these lung parasites has not been determined. All the writers upon this subject discredit the theory of direct transmissibility from one animal to the other of the same species. It would be contrary to all analogy. In the cases in question, where the mother cat had the infection and both of her kittens later developed the infection, one can explain the transmission by the fact that the mother and kittens ate of the same food.

In connection with the discovery of this case, the query, are we in danger of the spread of the infection among human beings? is a pertinent one. What danger are we in from eating raw vegetables in infected districts? May not some of our obscure pulmonary cases which have been diagnosed as tuberculosis be, truly, lung fluke infection, especially where the symptoms are not severe and where one is unable to find the tubercle bacilli in the stained sputum.

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BLOOD PLATELETS AND MEGALOKARYOCYTES IN HODGKIN'S DISEASE.[1]

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During the progress of a clinical and pathological study of Hodgkin's disease, which has been undertaken by the author in conjunction with Dr. J. L. Yates, of Milwaukee, certain features of the blood picture have been observed which seem worthy of note. They are of constant occurrence in the disease and appear characteristic of it. Before describing them it seems best to define the condition designated Hodgkin's disease so that there may be no confusion regarding the cases in the mind of the reader. The term is used in the sense of Reed, Longcope and Simmons to denote a non-tuberculous disease most common in young males (though by no means confined to them) characterized by a progressive enlargement of the lymph-glands, by a tendency to an anæmic state, by certain pressure symptoms and by a fatal termination, usually within a period of from three to five years. The lesion in the lymph-glands shows a progression from a hyperplastic cellular stage to a final condition of sclerosis. According to the terse and accurate description by Longcope[2] there is "an early increase in the lymphadenoid tissue with later proliferation of endothelioid cells, formation of uninuclear and multinuclear giant cells, thickening of the reticulum and a final overgrowth of connective tissue. Eosinophiles, though not specific, are frequently found in great abundance." To this might be added the fact that the architecture of the gland is early destroyed.

My first opportunity to study the blood of a Hodgkin's patient came at a time when I was engaged in an experimental study of the origin and of the relations of blood platelets and my attention was attracted by the remarkable platelet picture in the blood smears from the patient (Case I). The blood platelets of the smear were very well preserved and, stained by Wright's stain, showed the characteristic clear blue protoplasm with sharply cut border and with the central group of m tachromatic purplish granules. The platelets were exceedingly numerous. In fact I could not recall having seen any blood smear in which the number of platelets equalled that seen in this. In addition to this increase in number there was a striking variation in their size and shape. Many were round and approached the size of a red blood corpuscle. Oval forms also were found, from 15 to 20 μ in length and from 7 to 10 μ in width. Others took the form of pseudopodia, of about 4 μ in width and from 20 to 30 μ in length. From the sharpness of outline of these forms and the arrangement of their granules there was no question of their being due to the fusion of platelets. The picture was entirely different.

At a subsequent visit from the patient, who had in the intervening four months been under treatment with the X-ray, the same striking picture was present in the blood smear, and a count of the platelets by the Pratt method showed their number to be 1,140,000 per cmm.

Since seeing this case I have had opportunity to examine blood smears from eight other cases and to count the platelets in two of them. It does not seem necessary to report the cases in detail at this time, as clinical reports of the majority of them will be made in a subsequent paper. In addition to

[1] Paper read before the Association of Pathologists and Bacteriologists, May 3, 1910.

[2] Bull. Ayer Clin. Lab., 1903, No. 1, p. 4.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

the brief outline of the cases here given it should be said that with one exception (Case VII) the clinical diagnosis of Hodgkin's disease has been confirmed by the examination of a gland removed for that purpose. The cases are briefly as follows:

CASE I.—Nov. 20, '08 (Dr. Yates). Male, white, 21 yrs. Onset in July, '08. Cervical and axillary glands involved. Oct. 30, '08, gland removed for diagnosis showed early Hodgkin's changes.
Nov. 20-08. R. b. c., 5,304,000; w. b. c., 7500.
Mar. 4-09. R. b. c., 4,968,000; w. b. c., 4800; platelets, 1,140,000.
June 11-09. R. b. c., 5,600,000; w. b. c., 7000; platelets, 475,000.
Feb. 16-10. R. b. c., 5,800,000; w. b. c., 7000.

CASE II.—Nov. 10, '08 (Dr. Yates). Male, white, 10 yrs. Large mass of discrete glands in left cervical region of at least one year's duration. Test gland showed well-marked Hodgkin's picture. Glands removed at operation Nov. 10, '08.
Apr. 1-09. R. b. c., 4,712,000; w. b. c., 9500; platelets, 750,000.
Jan. 22-10. R. b. c., 5,250,000; w. b. c., 9600.
Oct. 8-10. R. b. c., 4,960,000; w. b. c., 9800; Von Pirquet test neg.

CASE III.—Apr. 1, '09. Male, white, 30 yrs. Seen two weeks after second operation for enlarged glands of neck. First operation six months previous at Rochester. Diagnosis Hodgkin's disease.
Apr. 1-09. R. b. c., 4,560,000; w. b. c., 10,000; platelets, 720,000.

CASE IV.—Feb. 5, '10 (Dr. Tupper, Eau Claire, Wis.). Female, white, 40 yrs. Eight months previously right inguinal glands began to enlarge. Two months later left inguinal and left axillary glands; four months later left cervical glands and one in right cervical region. Test gland showed advanced Hodkgin's lesion.

CASE V.—Nov. 9, '09 (Dr. Yates). Male, white, 8 yrs. Swelling of cervical glands began five months ago; on date left inguinal glands also enlarged. Test gland showed early hyperplastic stage of lesion.
Nov. 9-09. W. b. c., 9900.
Jan. '10. Left cervical group of glands removed.
Feb. 26-10. R. b. c., 5,000,000; w. b. c., 5000.
Oct. 8-10. Von Pirquet test negative.

CASE VI.—Mar. 10, '10 (Dr. Sullivan, Madison). Male, white, 16 yrs. Marked involvement of left cervical glands. Had been noted for only one month. Examination of test gland suggested greater duration, from the sclerosis and advanced condition of the lesion.
Mar. 10-10. W. b. c., 18,000.

CASE VII.—Jan. 5, '10 (Dr. Bennet, Oregon, Wis.). Female, white, 64 yrs. Onset in inguinal glands, March, 1909.
Oct. 24-09. General glandular enlargement with clinical diagnosis of Hodgkin's disease.
Jan. 5-10. R. b. c., 3,200,000; w. b. c., 4450.
June 30-10. Death from exhaustion and anæmia.

CASE VIII.—(Dr. Yates). Male, white, 33 yrs. Onset in March, '07 with supraclavicular glandular enlargement.
Sept., '08. Left supraclavicular and left axillary glands most enlarged. Some enlargement in right cervical, axillary and inguinal region.
Oct. 30-08. Excised gland shows typical and advanced Hodgkin's lesion.
Jan., '09. Blood smears examined.
May 20-09. Patient died.

CASE IX.—Oct. 3, '10 (Dr. Yates). Male, white, 5 yrs. Left cervical glands markedly enlarged. Five months duration. Test gland shows marked Hodgkin's changes.
Oct. 3-10. R. b. c., 4,800,000; w. b. c., 4200.

In the two cases in which the platelet count was made (Cases II and III) the counts were as noted, 750,000 and 720,000 respectively, numbers which are well above the limits ordinarily given as normal. While three counts form a limited number on which to base a statement that the platelets are increased in Hodgkin's, I am relying also on the appearance of the stained smears from the six cases uncounted. Comparison of these six with blood smears from the three cases counted and with smears from normal individuals shows that in the Hodgkin's cases there is a definite increase in the platelets. There was no exception to this finding in the series. Furthermore, as constant as this finding, is that of platelets of unusual size and of the pseudopodia-like masses. These latter have varied much in size and shape, the longest approximating 50 μ in length. Their staining is identical with that of the platelets. The distribution of granules and the sharp borders preclude the possibility of their being fused platelets. Their general character can best be indicated by reference to the camera lucida drawings of a few specimens shown in Figures 1-4. My experience with these cases leads me to believe that these masses and pseudopodia are so frequent that one can scarcely fail to find them in any smear from an active case of Hodgkin's disease. On the other hand, in searching for them in the blood of normal individuals, I have found but one small pseudopodium in a careful examination of blood smears from fifteen individuals.

The question naturally arises: What is the nature of these masses which take the platelet stain? I have spoken of them as pseudopodia as I find they are identical in form and staining reactions with the specimens of Wright and with the figures published in his demonstration of the origin of platelets from the megalokaryocyte pseudopodia.[3] Further, as I have indicated in a previous paper,[4] I have been able to confirm Wright's findings in the rabbit and have found similar pseudopodial masses in the capillaries of the bone marrow and of the lung. I think it can be stated definitely, therefore, that these masses of platelet nature observed in cases of Hodgkin's disease are masses of megalokaryocyte protoplasm and of unconstricted pseudopodia of the same.

In an attempt to explain why these pseudopodia should be found in the peripheral blood stream in such numbers, while they are very infrequent in the peripheral blood of normal individuals, my attention was directed by previous experimental work to the lungs. Investigations carried on upon the rabbit had shown that when platelets are being rapidly produced megalokaryocytes in considerable numbers leave the bone marrow. A majority of these are held up in the lung capillaries where their nuclei form thrombi, while their protoplasm is stripped off and forms the pseudopodial masses and the large forms of platelets found in the rabbit in this condition of rapid platelet production. Other megalokaryocytes slip through the lung and may be found in other organs, particularly in the spleen and in the liver.

[3] J. Morph., 1910, XXI, 2.
[4] J. Exp. Med., 1909, XI, 541.

Through the kindness of Dr. W. H. Welch and of Dr. W. T. Longcope I have been able to examine the lungs of four cases of Hodgkin's disease from the pathological collection of the Johns Hopkins Hospital, and the tissues, including the lungs, from seven autopsy cases from the Pennsylvania Hospital. In none of these eleven lungs, in sections taken from parts uninvolved by the disease, were megalokaryocyte nuclei lacking. In four of the eleven cases they were much more numerous than ever found to be in the human lung in cases of marked leucocytosis, in which their presence to some degree is constant. It is impossible to give exact mathematical values to the numbers in the various lungs because of the varying alveolar expansion in the different specimens. An idea of their frequency may be gained, however, from the statement that in one lung, that of autopsy A-324 (Penn.), no field of moderate magnification (Zeiss: obj., 8; oc., 8) showed absence of megalokaryocytes and the number in such fields varied from three to twelve. Examination of sections of other organs revealed an occasional megalokaryocyte nucleus in the capillaries of liver and spleen—but in no case were they numerous.

That these megalokaryocytes in the lung capillaries come from the bone marrow seems to me certain. There is but one other remote possibility. Examination of a considerable series of gland sections from cases of Hodgkin's disease from a variety of sources, shows that in well advanced cases there is present in the glands, besides the endothelioid giant cells, a type of giant cell indistinguishable from the bone marrow megalokaryocyte. Whether these giant cells are formed *in situ* or are bone marrow giant cells is undetermined. If they should escape into the lymphatics they would also be held up in the lungs. Yet they are so soon enclosed in a fibrous network that their escape in any such numbers as indicated by the lung sections appears improbable. Furthermore a study of bone marrow sections from five of the Pennsylvania series of autopsies seemed to show a definite increase in megalokaryocytes in three. In one was noted an unusual number of small megalokaryocytes, the young forms, showing an activity in this type of tissue in the marrow. All these features with the analogy of the rabbit findings leave, I think, no question as to the origin of the giant cells found in the lungs.

One other bone marrow feature was of interest. In addition to a more extensive pyknosis of giant cell nuclei than is commonly seen, in four of the five marrows was found karyolysis in these cells. This was most marked in a marrow in which there was necrosis of other marrow elements (Penn. Aut. 523), but occurred in the other three marrows where no necrosis of other elements was noted.

In conclusion the findings here presented would seem to indicate that in Hodgkin's disease there is a special activity of the platelet-producing elements resulting in the production of large numbers of platelets and in the emigration of megalokaryocytes in large numbers from the bone marrow. In the lung capillaries these latter are stripped of their protoplasm, which appears in the peripheral blood stream in the form of the masses and pseudopodia described. What part this increased platelet production plays in the disease, I am unable to say. There is in the findings a suggestion that the toxin of the disease acts as sharply upon the megalokaryocytes as upon the lymphoid elements, leading eventually to their necrosis.

These findings are further submitted as additional evidence of the genetic relation between megalokaryocytes and blood platelets.

DESCRIPTION OF FIGURES.

Pseudopodia and megalokaryocytic protoplasm masses from Cases II, IV, V, VII. The figures are camera lucida drawings with the same magnification. The variation in size of the red cells is attributable to variation in the tension under which the smears were spread. In two cases (Figs. 1 and 3) the coverslip method was used in making the smears, in the other two (Figs. 2 and 4) the slide method.

PRIMARY GENERAL PERITONITIS WITH ISOLATION OF THE *BACILLUS LACTIS AEROGENES* IN PURE CULTURE FROM THE PERITONEAL EXUDATE.

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Interest in the capsulated group of bacilli (*B. mucosus capsulatus*) has largely centered in the discussion as to the identity of the different members of the group with one another. On this single point a large literature has sprung up, but the question is still to be regarded as only approximately settled. Friedländer's[1] announcement of the discovery of his organism was promptly followed by publications reporting similar, but not identical organisms. These included the rhino-scleroma bacillus (Fisch, Paltauf, and Eiselsberg), the ozaena bacillus (Loewenberg and Abel), the *B. lactis aerogenes* (Escherich) and many others (Fasching, Pfeiffer, von Dungern, etc.). Indeed, Ficke was able to collect from the literature, twenty-two varieties of the organism to which Fraenkel has given the collective name *B. mucosus capsulatus*. There have been many efforts to simplify the matter by showing the identity of some of these forms with one another and reducing them to a few group types. Unfortunately this has not proved an easy matter. Nor has it been possible to simplify the question by applying the serum tests; for all attempts at agglutination have so far failed. (Landsteiner[2]).*

* Von Eiseler and Porges (Centralbl. f. Bakteriol., 1906, XLII, p. 660) claim to have differentiated the ozaena bacillus and rhino-scleroma bacillus from the bacillus of Friedländer by agglutination and precipitation with immune sera.

While there cannot, then, be said to be complete agreement on the subject the conclusions of Wilde represent approximately the majority opinion of bacteriologists; and they have the very great value of standardizing these organisms so that intelligible description of the various forms is possible.

Wilde[5] assembles the numerous varieties of the *B. mucosus capsulatus* under five type groups with the following distinguishing characteristics:

1. Type: *B. lactis innocuus.*

Raised, rounded, porcelain-like colonies on gelatin plates, or colonies like those of *Bact. coli.* No gas formation in glucose agar, alkali formation in milk-sugar bouillon, no coagulation of milk, no indol formation, grey-brownish growth on potato (without formation of gas), very slight pathogenicity for animals.

2. Type: Scleroma bacillus.

Mucoid, raised, colonies on gelatin plates, no gas formation in glucose agar, no (or very slight) acid formation in milk-sugar bouillon, no coagulation of milk, no indol formation, bright grey, translucent growth on potato (occasionally with acid formation), moderate pathogenicity for animals.

3. Type: *B. pneumoniae Friedländer.*

Raised, porcelain-like colonies on gelatin plates, gas formation in glucose agar, acid formation in milk-sugar bouillon, no coagulation of milk, no indol formation, creamy yellowish growth on potato (usually with marked acid formation), moderate or great pathogenicity for animals.

4. Type: *B. aerogenes.*

Raised, or flat, colon-like colonies on gelatin plates, abundant gas formation in glucose agar, acid formation in milk-sugar bouillon, coagulation of milk, no indol formation, abundant growth on potato (with gas formation), marked pathogenicity for animals.

5. Type: *B. coli immobilis.*

Flat, colon-like or raised colonies on gelatin plates, gas formation in glucose agar, acid formation in milk-sugar bouillon, coagulation of milk, formation of indol, gas formation on potato variable, moderate or marked pathogenicity for animals.

From this it will be seen that the bacillus of Friedländer is not regarded as identical with the bacillus of scleroma but is distinguished from it by its ability to form gas in glucose agar; nor with the *B. lactis aerogenes,* which has the power (not possessed by the bacillus of Friedländer) of coagulating milk. Wilde recognizes the existence of intermediate forms; but thinks the attempt to distinguish them as separate species unnecessarily confusing; and suggests these rather sharp distinctions as a useful basis for description. Strong[4] attempts even greater simplification by recognizing only two groups, as follows:

1. Friedländer Group: Easily stained capsules, in tissues and exudates; pseudo-capsules occasionally in artificial media: gas production most abundant on saccharose; slightly less on glucose, little or none on lactose: *no coagulation of milk.*

2. Aerogenes Group: Capsules difficult to stain and inconstant; no pseudo-capsules in artificial media: more abundant and constant gas formation on all three media; *rapid coagulation of milk:* equal amounts of acid on all three sugars.

Grimbert and Legros[5] go even further, claiming that the bacillus of Friedländer and *B. lactis aerogenes* are identical. All forms of both bacilli which they examined coagulated milk in from forty-eight hours to five days; and they cite Denys and Martin[6] as having shown that the bacillus of Friedländer, even if unable to coagulate milk at first, may acquire this characteristic by successive passage through this media.

It will thus be seen that there is justification for regarding the various members of the capsulated group as nearly, if not quite, identical; but that if any distinction is to be made a capsulated bacillus which produces gas in glucose and coagulates milk should be called the *B. lactis aerogenes.** This has been my warrant for the name given to the organism here reported as found at operation in the exudate of a primary peritonitis.

Though the specific nature of the bacillus of Friedländer as the cause of croupous pneumonia could not be established, the pathogenicity of the capsulated group has long been recognized. For laboratory animals it has often been found fatal, though its variable virulence has been again and again emphasized. The discussions as to the distinctions between the various members of the group have rather overshadowed interest in its relation to human disease; but isolated reports of its occurrence in various pathological conditions have continued to appear. In 1895 Étienne,[7] a year later Hébert[8] and two years later Léon[9] collected the literature on this subject. None of these publications are absolutely complete; and several reports of the occurrence of a capsulated bacillus in human disease have since appeared.

The following table contains a complete list of the diseases from which the *B. mucosus capsulatus* has been isolated and thus renders the literature on its pathogenicity readily accessible:

TABLE.

Diseases from which the *B. mucosus capsulatus* has been isolated. The organism has been reported as the bacillus of Friedländer; but also as the rhino-scleroma bacillus, and the *B. lactis aerogenes.*

Aphthous stomatitis (Cited in review by Étienne[7]).	
Purulent rhinitis.	"
Rhino-scleroma.	"
Purulent parotitis.	"
Purulent dacryocystitis.	"
Ulcer of the cornea.	"
Phlegmon of the orbit.	"
Purulent otitis media.	"

* Or, *B. coli immobilis,* according to Wilde; the two are distinguished by the ability of the latter to form indol.

Bronchopneumonia (Cited in review by Étienne[7]).
Empyema (Dieulafoy[42] has reported pyopneumothorax due to gas-producing organisms, without any connection with the lung). "
Serous and purulent pericarditis. "
Simple and purulent meningitis. "
Angiocholitis. "
Pyelonephritis. "
Pyaemia. "
Septicaemia. "
Ulcerative endocarditis. "
Acute lobar pneumonia (Curry[10]).a
Gangrene of the lung (Fortineau[11]).
Membranous bronchitis (Léon[9]).
Osteomyelitis (Schlagenhaufer[12]).b
Abscess of the brain (Sachs[13]).
Pseudo-membranous angina (Hébert[8]).
Salpingitis (Schenk[14]).
Endomyocarditis (Josserand and Bonnet[15]).
Abscess of scrotum (Halban[16]).
Cystitis (Montt-Saavedro[17]).
Purulent conjunctivitis (Kiesentzki[18]).
Empyema of Antrum Highmorii (Howard[19]).
Epidemic exfoliative dermatitis (Russell[20]).c
Hemorrhagic sepsis (Blumer and Laird[21]).d
Hemorrhagic sepsis of new-born (von Dungern[22]).e
Typhus exanthemicus (Hlava[23]).
Cholecystitis (Christian[24]).
Bacteriuria (Wartburg[25]).f
Liver abscess (Ranzi[26]).
Peri-deferential abscess (Macaigne and Vauverts[27]).
Gastro-enteritis (Fricke[28]).g
Tonsillitis (Curry[29]).
General gaseous emphysema with gas cysts of brain (Howard[30]).h
Peritonitis.i

There is then, abundant justification for Hébert's claim that the bacillus of Friedländer must be included in "la catégorie des microbes à tout faire"; and that, along with the staphylococcus, the streptococcus, *B. coli communis*, and *B. pyocyaneus*, *B. mucosus capsulatus* must be regarded as a saprophyte which becomes an infectious agent when its virulence is increased or the resistance of the host diminished.

It is striking that in the lists, given by Hébert, and by Léon of pathological conditions caused by the capsulated bacillus, no mention is made of peritonitis; and it is certain that a peritonitis of this origin must be both relatively and absolutely, quite rare. The present case is unique in that the *B. lactis aerogenes* was grown from the peritoneal exudate during life in a case of primary peritonitis. The word "primary" is used in the sense of Flexner[31] who suggested this term for that interesting group of cases in which an "inflammation (usually diffuse) of the peritoneal cavity occurs without the mediation of any of its contained organs"; or without any operative or other interference. It may arise independently (spontaneous peritonitis) or may accompany infections in distant parts of the body. Twelve of the one hundred and six cases examined by Flexner at autopsy, were of this variety; and the condition, though a rare one, is well recognized by surgeons.

Onset of illness suddenly two weeks before admission; acute, severe abdominal pains with nausea but no vomiting; then continuous pain, with exacerbations. No jaundice. T. 105.5° F. P. 120. Leucocytes 17,000. Pelvic examination negative. Signs of general peritonitis. Diffuse exudate found in peritoneum at operation. No source found for the infection. Appendectomy, drainage. B. lactis aerogenes in pure culture from the peritoneal exudate. Blood cultures negative. Slow convalescence; pulmonary complication (probably tuberculosis). Recovery.

History.—The patient was an unmarried colored girl, eighteen years old, a nullipara, with normal menstrual, and negative previous history. Two weeks before admission she had been suddenly awakened by severe, knife-like epigastric pain. This soon subsided, but some abdominal pain had been present from the onset to the time of admission to the hospital; and there had been several returns of the acute paroxysms experienced on the first night of the illness. She had also complained of some pain in the left hypochondrium. She had never vomited, but had been slightly nauseated. No jaundice.

On admission, the patient was suffering intensely from abdominal pain. Temperature 105.5° F., pulse 120, leucocytes 17,000. The abdomen was uniformly distended and the respiratory movements greatly restricted throughout. No visible peristalsis. The left lower quadrant was free from tenderness, which was, however, present in the left upper quadrant. Very slight rigidity of the rectus and oblique muscles on the left side. There was definite tenderness throughout the right side—quite marked at MacBurney's point (where there was muscle-spasm), but so exquisite in the right upper quadrant and accompanied by such spasm of the rectus as to make further palpation here impossible. No mass could be felt anywhere. On percussion, dulness was made out in both flanks; the rest of the abdomen was tympanitic. The liver margin was about 1 cm. above the costal margin in the right mammillary line. There was a profuse vaginal discharge (containing Gram negative intra-cellular diplococci) and ulcers on the labia. The vulva was marital but pelvic examination was negative. An exploratory laparotomy was immediately done through a right rectus incision. A considerable quantity of turbid fluid was found free in the peritoneal cavity. The abdominal viscera were uniformly injected, but there was no fibrin present, though the serosa of the intestines was quite red and did not glisten. The appendix and gall-bladder shared in the general inflammation; but were otherwise normal. The Fallopian tubes were quite red, but not distended and no pus could be pressed from their fimbriated extremities. The appendix was removed and two drains placed in the pelvis. Two days after the operation the patient began to cough. Her temperature re-

a The relation of the organism to pneumonia is here discussed.

b Streptococci were also found in the smears from this case; but the bacillus of Friedländer grew out in pure culture.

c The organism found was similar in many, but not in all, respects to the bacillus of Friedländer.

d The cultures were made after death.

e The bacteriological report is very deficient.

f Appeared with fever, chills and headache; symptoms left in three days; bacteriuria finally disappeared under urotropin.

g Organisms found in the stools; presence of B. Friedländer as normal saprophyte in the intestines doubtful; Fricke, Lembke, Germano and others were unable to find it.

h Perkins (J. Exp. M., Jan., 1901) reports a laboratory epizootic among guinea pigs, associated with emphysema of liver, spleen and kidneys, from which the *B. mucosus capsulatus* was isolated.

i These cases receive separate consideration below.

mained elevated, and convalescence proceeded very slowly. The peritoneal symptoms gradually diminished; but signs and symptoms of lung involvement increased.

Blood cultures were done on two occasions, and were negative, as was also the Widal test.

One month after the operation she was transferred to the medical service. Her operative wound was then practically healed, her peritoneal condition negative; but there was a persistent cough with profuse, pale green muco-purulent expectoration. Her leucocytes were 12,600. Her respirations were rapid and shallow, expansion was limited over the left upper front; the percussion note was high pitched in the inter-scapular region, below the angle of the scapula, and in the lower axilla. There was also some impairment over the lower right lobe. The breath sounds were harsh over both fronts, enfeebled over the backs below the spines of the scapulae, but nowhere absent. Expiration was prolonged and numerous fine râles were heard. The patient gave a first degree positive reaction to tuberculin in the left eye. Repeated examinations of the sputum for tubercle

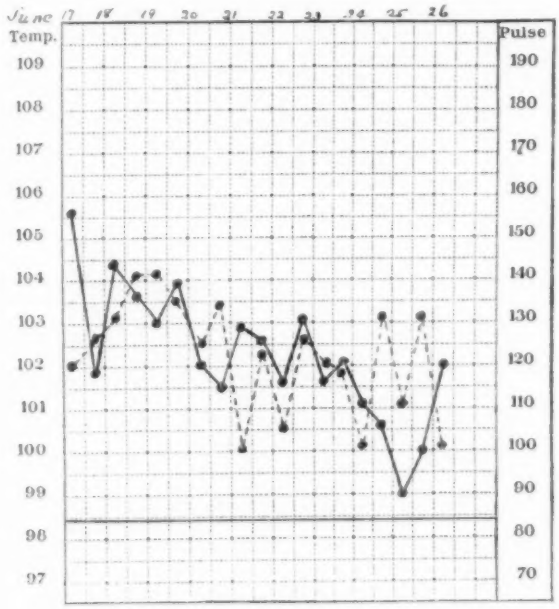

Chart for First Ten Days After Operation.
Solid line = temperature.
Broken line = pulse.

bacilli were negative. The Wassermann test was also negative.

The patient slowly improved and was discharged with a normal temperature, though signs of lung involvement persisted.

The accompanying charts (condensed from the regular temperature and pulse charts of the first and the final days of her illness), indicate the course of the disease.

Cultures made from the peritoneal exudate at operation showed an abundant, dirty whitish growth on agar. The organism was a bacillus of varying size, non-motile and Gram negative. Capsules were readily stained. Gas was formed on potato and in glucose agar. After forty-eight hours, there was acid formation in milk but no coagulation. Slight coagulation occurred in five days; complete coagulation in nineteen days.

This finding, though rare, is not entirely without precedent. No one, however, has reported the organism from a primary peritonitis in cultures made during life.*

The cases of peritonitis, to be found in the literature, in which *B. mucosus capsulatus* was reported as the cause are the following:

1. Breinl[22]: Great hyperplasia of the lymphatics of the small intestine; death from intestinal perforation. In the pus a capsulated bacillus was found which was Gram negative but did not coagulate milk. It was pathogenic for white mice.

2. Fraenkel[23] reports the bacteriological findings (apparently at autopsy) in thirty-one cases.

The following members of the capsulated group were found:

B. lactis aerogenes.

1. Peritonitis from perforation of caecum.
2. Peritonitis with suppurative cholecystitis.

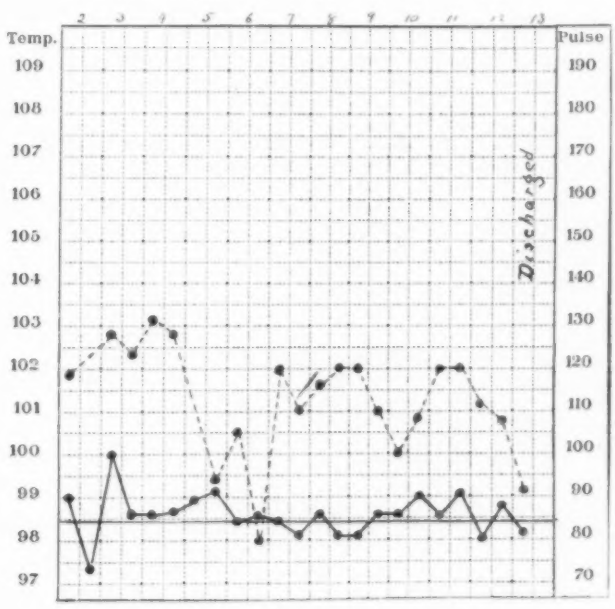

Chart for Last Days of Illness.†
Solid line = temperature.
Broken line = pulse.

B. lactis aerogenes with a *Diplococcus pneumoniae.*

3. Sero-fibrinous peritonitis with nephritis.

Organism resembling *B. lactis aerogenes.*

4. Purulent peritonitis with pyelo- and para-nephritis.

3. Howard[19]: a. Male dead after castration. Multiple abscesses of both kidneys; peri-rectal abscesses opening into cul-de-sac; fibrinous peritonitis. Cultures from peri-rectal abscess, peritoneum, heart's blood, spleen and renal abscesses

* There is good reason for supposing that all the cultures in Howard's cases were taken post mortem, though it is not, I think, definitely so stated.

† The high pulse throughout may have been accounted for by the enlargement of the thyroid which was present. There was also a definite tremor of the hands and a von Graefe's sign.

showed a capsulated bacillus, *which did not decolorize by Gram.* (Decolorization by Gram's method is an essential characteristic of this group of bacilli.)

b. Girl with chronic peritonitis; peritoneal cavity contained large amount thick, creamy pus from which a pure culture of the bacillus of Friedländer was obtained. (It is not stated that this culture was obtained post mortem; nothing said about appendix or tubes, or as to the origin of the infection.)

c. Man, dead of acute croupous pneumonia. Acute general fibrino-purulent peritonitis found. Cultures from pneumonic areas, peritoneum (and elsewhere) showed the bacillus of Friedländer.

d. Ranzi [26]: In the case of liver abscess already referred to (multiple liver abscesses, general peritonitis and endocarditis were found at autopsy), the bacillus of Friedländer was isolated in pure culture from the abscesses, the peritoneal exudate and the cardiac vegetations.

The rarity of this organism in peritoneal infections is illustrated by its absence from the series of one hundred and six post mortem examinations reported by Flexner.[31]

In addition to its other better known pathogenic properties the *B. mucosus capsulatus* is, then, to be thought of in connection with five groups of cases.

1. *Peritonitis.* Cases of Breinl, Fraenkel, Howard, Ranzi [a] and Churchman.[b]

2. *Hemorrhagic Sepsis* (Infectious purpura). Cases of Blumer and Laird, Howard,[34] Neumann,[35] von Dungern [22 c] and Léon.[9]

3. *Liver Infections.* Cases of Ranzi, Canon,[36 d] Wicklein,[37 e] Kockel,[38 f] Wright and Mallory,[39 g] Clairmont [40 h] and Étienne.[7 i]

5. Pseudo-membranous angina.[k]

6. Diseases of the Eye.[l]

This patient was treated in the service of Dr. W. S. Halsted, to whose liberality I owe the opportunity of reporting the case. To the kindness of Dr. C. G. Guthrie, I am indebted for the bacteriological examinations made.

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[a] In these four the organism was found post mortem.

[b] Organism found during life.

[c] Bacteriological report deficient.

[d] Septicaemia starting from abscesses of gall-tracts.

[e] Organism reported as bacillus of Pfeiffer.

[f] Multiple infected liver cysts.

[g] Liver abscess following appendicitis and thrombosis of portal vein. Bronchopneumonia.

[h] Peri-cholecystitic abscesses and acute cholangitis.

[i] Mentions unpublished case of Neller (angiocholitis).

[k] Paris Thesis of Hébert [8]

[l] Perles [41] has demonstrated the marked pathogenicity of the bacillus of Friedländer for the eye. Kiesentzki [18] has reported a case of double purulent conjunctivitis in the new-born due to this organism; and Gourfein,[42] in an experimental research on the rôle of Friedländer's bacillus in ophthalmology found the organism in five per cent of four hundred and fifty cases of conjunctivitis, and in ten per cent of forty cases of dacryocystitis.

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THE SUBMUCOUS RESECTION OF THE NASAL SEPTUM, TECHNIQUE AND RESULTS IN THE WRITER'S PRACTICE.*

By Sylvan Rosenheim, M. D., Baltimore.

The development of this operation rests on principles practiced long before the operation attained any great vogue. Various orthopedic methods had been used to correct these nasal deformities. Many surgeons, among them Trendelenburg, Roux, Juracz and others attempted corrections, using the submucous method. For instance, Trendelenburg separated the movable septum from the upper lip, dissected up the mucosa, and then resected a small piece of cartilage. Among rhinologists Hartman submucously removed in the early days a small piece of cartilage. Peterson did the same making a flap with the base upwards.

To Krieg, however, belongs the credit of putting the operation on a sound basis. His first publication appeared in 1886. His second report in 1889 records 14 cases and improvements in technique. In his third report in 1900 he gives the results of 130 operations and refers to the non-recognition of his work. Krieg's operation consisted in a removal of the deflected cartilage and bone with the sacrifice of the muco-perichondrium and periosteum of one side. He considered the operation at all times very difficult, at times a veritable "Kunststück." The after treatment took a number of weeks; but the results were excellent and in 50 per cent of the cases, external deformities were corrected. There were perforations of the septum in 12 per cent of his cases. In 30 per cent of the cases a preliminary treatment, usually cauterization of the inferior turbinate, rarely resection, was necessary.

Until 1899 the method had not been extensively used as is evidenced by Victor Lange's statement in Heymann's Handbuch that there was no good operative method for the correction of septal deformities. In this year Bönninghaus reported 19 cases and stated that he had been using this method for the last four years. He lays emphasis on the importance and necessity of also removing the bony parts of the deviation. The discovery of the properties of an aqueous extract of the suprarenal capsule on the vascular system by Schaefer and Oliver and others and further work along this line by Abel was quickly followed by the clinical use of this substance. This discovery materially aided the development of this operation as it did of all other operative nasal work.

In America, Otto T. Freer developed this operation along original lines. His first publication in the Journal of the American Medical Association gives E. F. Ingals (1882) credit for originating the type of operation designated by Krieg as the window resection. Freer's work was started in 1901 and he was ignorant of the previous work of Krieg and Bönninghaus. Freer's original method consisted in the making of flaps, the anterior one being held forward so as to thoroughly expose the deviation, and after dissection of the mucosa, in removing the cartilage. He then fractured the cartilage and placed it in a straightened position. In his later publications he states that he has given up the practice of fracturing the bony septum, and instead cuts it away with Grünwald's forceps. For this work he has devised 12 knives which are found to be most useful and necessary. In speaking of making the flaps he speaks of dissecting the mucosa but he probably includes the perichondrium and periosteum in this flap. Comparing this operation with the Asch method, he says "the latter will always be resorted to by the general surgeon who enters special fields without special skill, for the surgeon sins against us far more than the cautious general practitioner anxious for his patient's welfare."

Killian in 1904 published his most exhaustive paper giving the whole detail of the operation in his hands and the results of his cases. His paper marks an important milestone in the development of the operation, inasmuch as most operators at the present time use essentially his method. In a previous paper (1899) he had pointed out that the making of a flap and the use of his long speculum for "rhinoscopia media" materially helped in the operation and lessened the after treatment. He lays great stress in a strict aseptic technique and draws attention to the various contra-indications to the operation. Killian makes a vertical incision about one-half a centimeter behind the movable septum. This incision goes to the cartilage. He next elevates, laying stress on the importance of including the perichondrium in the part elevated. He next perforates the cartilage, using a finger in the other side of the nose to prevent going all the way through to the other side. After elevating the muco-perichondrium of the other side he removes the cartilage with his own cartilage knife or with Hartman's biting forceps. A picture of his cartilage knife readily demonstrates that Ballenger's swivel knife is practically the same with the exception that the knife revolves. Posteriorly the bone is removed with Hartman's biting forceps, anteriorly with Killian's chisel. If necessary the flap is sutured.

About the same time Hajek, Menzel and others published the results of their work and their methods, but they added nothing to that of Killian, in fact they hardly seemed to realize the beauty and the superiority of his work.

From this time on these methods of operating on deformed nasal septa increased in popularity. They were rather late in getting to England notwithstanding its proximity to the country where it originated and was rather extensively used. For instance, in 1901 Mayo Collier remarked that he had seldom or never attempted to straighten the septum; the results were most unsatisfactory, and he preferred to remove a piece with knife, chisel or saw. In 1904, St. Clair Thomson described his results in a number of cases.

There have been various improvements in technique in the

* Paper read before The Southern Section of the American Laryngological, Rhinological and Otological Society, Jan. 21, 1911.

last few years. Ballenger's swivel knife, a modification of Killian's cartilage knife, has simplified the removal of the cartilaginous septum. Hurd, Beck, Carter, Bruning and others have devised various instruments that assist in the operation. To prevent perforations, Gulliver transplants a piece of muco-perichondrium from the redundant side in the perforated spot and holds it there with packs. Ballenger describes another method of avoiding a permanent perforation, which he says he learned from Dr. Goldsmith of Toronto. After resecting the cartilage it is placed in normal salt solution and if there is a perforation produced during the operation, a piece of this cartilage is placed and held there by packs. Yankauer's suggestion to extend the vertical incision across the base of the nose, aids considerably in enlarging the field of operation.

Writer's Method of Submucous Resection of the Deviated Nasal Septum.

The patient enters the hospital on the morning of the operation, undergoing a thorough physical examination. The urine is examined for albumin and sugar. One-half hour before the operation there is administered a hypodermic of one-quarter grain of morphia.

Instruments.—The following instruments are used: Beckman's nasal speculum, probe, applicators, Freer's right and left angular and straight knives, Freer's sharp and dull elevator, Jansen's dull elevator, the writer's specula, Ballenger's swivel knife, Grünwald's and Jansen's biting forceps, Killian's chisel and hammer, dressing forceps, and Worthington's membrane holder.

Technique.—Two nurses are used, and the instruments are sterilized by boiling, the head mirror by the use of formalin vapor. [Photographs show the arrangement of the room and table.] The patient's face is washed with soap and water, alcohol, and bichloride solution. A sterile towel is placed around the head and a sterile sheet covers the body.

Operation.—The septum is cocainized with swabs placed first in adrenalin chloride solution 1-1000, wrung dry and then dipped in powdered cocaine. This is rubbed on both sides and also on the turbinates if these are to be removed at the same time, and in the antral, ethmoid and sphenoid regions, if a sinus operation is also to be performed. Cocainization is very rapid and the writer has not seen a single case of cocaine intoxication by this method in over five years' use of cocaine, whereas such was not infrequent by the pledget method of using cocaine. Also the anesthesia is much more profound especially where sinus work has also to be done. Rarely general anesthesia is necessary, ether being used. After cocainization, long pledgets soaked in a 1-1000 solution of adrenalin and wrung out almost dry, are packed against the septum of both sides and allowed to remain there from five to ten minutes.

The initial incision of Killian is made just in front of the deflected portion and continued outwards across the floor of the nose as suggested by Yankauer. This incision goes down to the cartilage and the muco-perichondrium and muco-periosteum of the convex side is then elevated with the various elevators described. The cartilage is next incised to the perichondrium of the opposite concave side. One soon learns to recognize when the perichondrium is reached and no special instrument or technique is necessary to prevent perforation at this point. If it occurs the method described by Ballenger of inserting a portion of the resected cartilage here can be used, although the author has had no occasion to try this procedure. Next the muco-perichondrium and muco-periosteum of the concave side are elevated. This is often much accelerated and rendered easier by the employment of the author's speculum which is next inserted, one blade on each side of the cartilage, and then opened up as far as possible. By the use of his speculum the field of the following steps is made most plain and visible and any injury of the membrane of either side is prevented (see cuts). The cartilage and bony deflected parts are then removed with Ballenger's swivel knife, Grünwald's and Jansen's biting forceps. The maxillary crest is removed with Killian's chisel. Where the deflection is very acute this method is slightly modified in that the cartilage up to the point of the deflection is first removed, and then the remaining part can be manipulated into a better position for continuing the dissection of the membranes. After all the deflected parts of cartilage and bone are removed the wound is thoroughly cleaned of debris with cotton sponges soaked in normal salt solution. The membranes are then smoothed down after removal of the speculum and the septum examined to find if straight or not. If it is not straight, it is due to insufficient removal of cartilage, bone or bony crest of the superior maxilla, which is removed until the septum assumes a vertical position. The membranes are held in position by Worthington's holder and a pack placed in each nostril, when the membrane holder is withdrawn. These packs are made of strips of iodoform gauze, surrounded with gutta percha protective and are greased with vaseline before insertion into the nose. A number of various degrees of thickness are made for each case and one that fits into the nares snugly is used on each side. They make most excellent packs, are withdrawn without any pain to the patient and without that bleeding which is so annoying after withdrawal of the ordinary gauze dressing. In case sinus work has been done, the protective covering of the pack is perforated in a number of places. If the ethmoid cells have been opened also, a small perforated pack is placed in this region superimposed on the other pack.

After his return to bed, the patient is given a glass of water, containing thirty grains of urotropin to the quart, every hour. He is put on full diet. If there is any headache he is given either migraine tablets, or a powder of acetanilid five grains, codeia sulphate half a grain, and one grain of caffeine citrate. If these are not efficient he is given a hypodermic of one-quarter grain of morphia. The next morning he is given a bottle of citrate of magnesia. The pack on the side opposite the incision is removed at the expiration of 24 hours, and on the side of the operation at the expiration of 48 hours. He is discharged from the hospital on the second day and after the packs are withdrawn is given a spray of Dobell's solution with

enough adrenalin chloride to make a 1-10,000 or 1-15,000 solution for home use. Usually but little after treatment is required in the simple cases. Where an inferior turbinectomy or a sinus operation is performed at the same time, it is necessary to irrigate the nose for some time afterwards.

Writer's Results.

The object of this paper is to give the results up to date in a series of cases in which he has performed this operation. His conclusions are based on his records of over fifty cases. Some earlier cases were dispensary cases of which he has no histories. Some of this small series were also dispensary cases but inasmuch as these received the same attention as the private cases, they are of equal value as statistics. Letters were written to all of the patients to return for examination to determine whether there had been any difference in the result as considered for a short time after the operation. Unfortunately only a small percentage have seen fit to appear (twenty-three). Letters have been received from seven which are of some value.

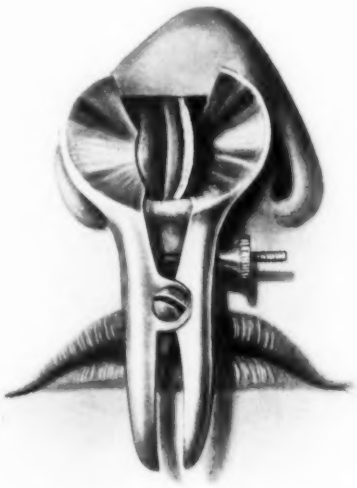

Fig. 1.—Speculum in place, before removal of cartilage and bone.

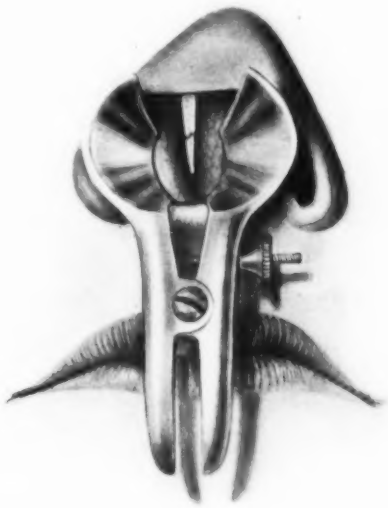

Fig. 2.—Deflected bone and cartilage removed. Posterior part of vomer and perpendicular plate of ethmoid visible.

I shall first enumerate the results in these cases at the time of their discharge and then give the further observations based on those patients who have returned for examination or who have written.

Regarding the ages of these patients, all but four of the early cases are over fifteen years of age. One patient was ten, another twelve, and two were thirteen years old. Owing to the fact that we do not know what effect this operation will have on the development of the nose, I have thought wisest not to operate on young children unless the breathing is absolutely cut off. In such cases it might be well to endeavor to improve the septal position by widening the palatal arch as suggested by Black, Brown, and others. So far I have seen but one of these young patients after the lapse of any time. This patient was a boy aged 13 years, on whom a submucous resection of the septum and later a double inferior turbinectomy was performed. Now, over three years later, the good result obtained at the time of the operation still continues; the breathing space is good, and the nose, he thinks, has rather improved in shape.

In about half of my cases a simple submucous resection was performed and in nearly all the rest either the inferior turbinate of one or both sides was removed in part. In one case, the anterior ends of the middle turbinates were resected. In three cases extensive sinus work was performed at the same time. In one case a hump on the dorsum of the nose was also removed by an external incision.

Reaction Following Operation. Infection.—I had always considered the submucous resection of the septum, an operation with no risk of mortality until I received a report from H. Hays, in which he described two cases of infection, resulting in one case in meningitis and death. Purcell also mentions one death following infection. As practically all these cases were done in the hospital the temperature charts have been at my disposal for accurate observation; also I have seen all of the cases for long enough times after the operation to make my following remarks absolutely accurate.

The temperature charts of my cases, to all but a few of which I have had access, show in most either a normal temperature or a rise of about one degree on the following day which quickly subsides after removal of the packs and clearing of the bowels. In one case the rectal temperature rose

to 102.5° F. and in another 103.4° F. but in these cases the temperature subsided in about 24 hours to normal after removal of the packs and calomel purgation. I have two cases of slight infection to report. In one case, an incomplete submucous resection was done by one of the house surgeons—his first case. Four days later the patient was readmitted to the hospital with a red swelling on the side of the nose which proved to be erysipelas, a mild attack, which quickly subsided. Examination of the nose revealed an incomplete removal of the cartilage and a small perforation of the septum and the septum somewhat swollen. One month later a more complete submucous resection was performed with excellent result. The day following the operation, the temperature went up to 102.6° F. (rectal) but fell to normal in 24 hours. In another case there was a slight infection between the membranes with slight swelling and slight elevation of temperature. A small amount of grumous material was scraped out through the original incision and a counter incision made in the septum, a little posteriorly. This discharged pus for about a week and then closed, leaving a clean septum, with no perforation. This case has been attended by no other bad result—such as sinking of the bridge of the nose.

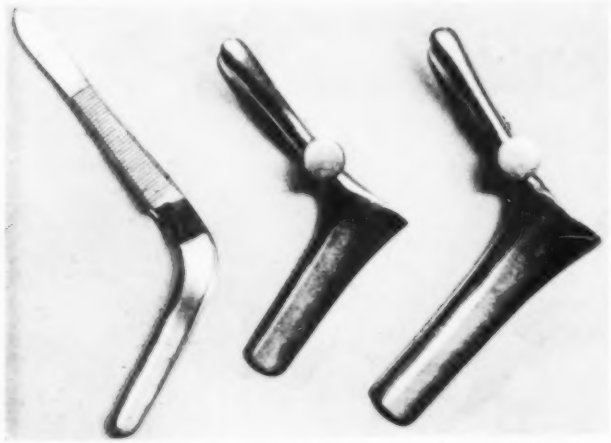

FIG. 3.—Worthington's flap holder, and author's speculum (two sizes).

Results in General.—In general, the results may be termed excellent. The main cause for this operation, difficulty in breathing through the nose, has been relieved in all cases but one, and in that case failure was due to a projection of the end of the quadrangular cartilage outside the nose on the side opposite the side of the deflection. This was not removed at the operation and on removal of the packs the cartilage reassumed a deflected position. Unfortunately this was an out of town patient and I have had no further opportunity to correct the work. The lesson from such a case is to operate from both sides, dissecting out the anteriorly placed deflection through an incision made in the cutaneous septum. Although no particular attempt was made in any of the cases to remedy external deformities, these were in many cases much improved as is shown by the rough casts of one case. These plaster casts are not difficult to make and once made, constitute an excellent method of ganging the result in this particular. In one case headaches were entirely relieved. A severe neuralgia of the side of the face to which the septum was deviated, has been entirely relieved for three and a half years following the operation in another case. A general improvement in health was noted by many.

Perforation of the Septum.—I have notes of perforations in four cases; three of which were very small and one being fairly large. In the last case, done some years ago, the deviation, as shown by the plaster cast, was very extreme, forcing outward the nasal bone of that side. I take it, however, that a perforation in this case could either have been avoided or would have been much smaller by using the method described earlier, namely, first removing the cartilage up to the point of deflection before attempting to dissect the membranes beyond this point. As has been the experience of others, I have observed no scabbing about these perforations nor have they given a patient, who is unaware of them, any discomfort.

Special Results.—One of the objects in reviewing these cases was to determine whether there occurred after the lapse of some time any bad after effects, such as sinking of the bridge of the nose. I also wished to get some evidence regarding the reformation of the cartilage and bone removed.

Depression of the Bridge of the Nose.—An early report by Sheedy of a number of cases of a sinking in of the nose following this operation made me particularly apprehensive in this regard. A later report by him is to the effect that now he seldom sees this deformity and thinks the former bad results were due to too extensive removal of cartilage. As the immediate result of the operation, I have not seen such a result. I have seen or heard from twenty-nine patients on whom I have operated from over four years ago to the present time. In not a single case was there a trace of any secondary sinking of the bridge of the nose. Several of these patients had syphilis which had been thoroughly treated and these did as well as any of the cases.

Reformation of the Septal Cartilage and Bone.—At the present time I can report on but eighteen cases in regard to this point. In all, the septum had regained firmness but in none could one say that there was complete reformation of the cartilage and bone. In some there was a large area, quite soft and movable to the probe; in others this area corresponded only to the center of the place from which the cartilage had been removed. Some of the more recent cases were firmer than the earlier cases. It is possible that this is due to not having included all of the perichondrium and periosteum in the early cases.

CONCLUSIONS.

1. The submucous resection of the nasal septum is a method by which all varieties of deflections of the septum can be corrected.

2. It is probably better for us to be cautious in the case of young children and do the operation only when it is urgently demanded.

3. Chronic sinus infections are not a contra-indication; in fact this operation is often a necessary accompaniment in order to complete the sinus work and obtain free drainage. Such operations as well as inferior or middle turbinectomies are best done at the same time.

4. Luetic individuals who have been well treated and show no signs of the disease, yield as satisfactory results as others.

5. It is absolutely essential to have strict asepsis in all the details of the work.

6. Infections following this procedure should be as infrequent as in any other operation carried out with aseptic technique, and the operation considered both safe and satisfactory.

7. Perforations of the septum may be caused infrequently but they are of no consequence and cause the patient no discomfort.

8. There is no reason to fear sinking of the bridge of the nose, following at any time after the operation. On the other hand, external deformities which may be present are frequently relieved.

9. While it is possible that there may be, to a slight extent, new cartilage or bone formed after the operation, this is never complete.

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THE GROWTH OF EMBRYONIC CHICK TISSUES IN ARTIFICIAL MEDIA, AGAR AND BOUILLON.

By Margaret Reed Lewis

and

Warren H. Lewis, M. D.

(From the Anatomical Laboratory, The Johns Hopkins University.)

In 1908, working under Dr. Max Hartman at the Kgl. Institut für Infectionskrankheiten in Berlin, one of us found that bone-marrow from the guinea-pig formed a membrane-like growth with mitotic figures on the surface of nutrient agar. This agar was a modification of one used at the Institute for the cultivation of amœba. In the place of distilled water a modification of Locke's modification of Ringer's solution was substituted.

Last fall we began the cultivation of embryonic pig bone-marrow in the blood plasma of older pig embryos. We utilized very much the same methods as were described by Burrows and Carrel, but without very conclusive results. We attempted to start our cultures from a very few cells instead of small pieces of tissue.

With the appearance of the important publications by Burrows and Carrel on the cultivation of the tissues of warm-blooded animals in clotted plasma adopted by Burrows from Harrison's brilliant discoveries on the growth of amphibian tissues, especially nerve axons in clotted lymph, we began similar studies on embryo chicks of various ages and were able to obtain by the method of Burrows and Carrel very wonderful growths from the various organs of the embryo.

The blood of adult chickens was used. It was taken from the external jugular vein, which lies just beneath the skin of the neck by means of a glass canula coated with paraffin, instead of oil, and was allowed to flow into paraffin-lined tubes, cooled in a freezing mixture, centrifugalized, the plasma drawn off and kept in paraffin-lined tubes in the ice box. We have obtained excellent growths with plasma two weeks old. Instead of sealing the hanging drops with paraffin, we find vaseline, which has been in the autoclave more satisfactory.

Not only were growths obtained in hanging drops, but much more extensive ones were obtained in Petri dishes, the diameter of these growths sometimes exceeding 1 centimeter. The Petri dishes must be kept in a moist chamber to prevent drying. The Petri dish method affords certain advantages for experimentation on the growth, which can be subjected to the influence of various fluids for varying lengths of time. We have obtained beautiful results with some of the vital stains, especially neutral red.

We have not found it necessary to dissect the chicks in a warm chamber, provided one works with sufficient rapidity in transplanting. Our observations have been made with the use of the warm stage, which seems quite satisfactory. Good growth takes place at temperatures varying from 34°–42° C.

There is great similarity in the growths from pieces of liver, intestine, heart, brain, kidney, adrenal, muscle, stomach, thyroid, retina, cornea, etc., of chick embryos from 10 to 21 days old. Radiating strands, migrating cells, membrane formations and vesicles or loop-like places seem to be common to all. The spleen, however, usually sends off migrating cells alone for some time after the culture is made, and only later do the radiating cells appear, if they appear at all.

The general similarity in the growths from the various organs seems to lead to the conclusion that the growing tissues are only such as are common to the various organs, namely, connective tissues of various kinds and endothelium of the blood vessels. We have been able to trace, in some fixed and stained specimens, the endothelium from the blood-vessels of the original piece out into the new growth where the cells of the endothelial radiations closely resemble the cells of the other radiations found there.

Recently we have succeeded in cultivating small pieces of embryonic chicks in a nutrient agar both in hanging drops and Petri dishes. The growths have, as a rule, not been so extensive as those in the plasma, but otherwise resemble them. Some specimens show radiations, others membranes and reticular formations with migration of cells. Mitotic figures are found in the stained preparations. The cells often show long irregular processes and move outward from the old piece. The following medium has so far given the best result with chick tissue:

Ringer		
NaCl	.9 gm.	
KCl	.042 "	
$CaCl_2$	.025 "	..... 10 cc.
$NaHCO_3$	.02 "	
H_2O	100 cc.	
Agar	.25 gm.	
Bouillon	.....	2 cc.
NaCl	.....	.0675 gm.

Into a hanging drop of this medium we transplanted two small pieces from the liver of a nine-day chick embryo. Within 24 hours cells began to radiate and migrate from the smaller piece into the surrounding medium. In 48 hours the growth had exceeded that of the control in plasma and was as extensive as any growth observed in plasma from such a small piece, less than ½ mm. in diameter. The entire growth at the end of 48 hours was four times the diameter of the original piece and could readily be seen with the unaided eye.

The specimen was fixed when 48 hours old in osmic acid vapor and stained with Ehrlich's hematoxylin and eosin. All stages of mitosis are present in the new growth; as many as 10 mitotic figures were counted in one field under the high power.

Small pieces of transplanted intestine, about 1 mm. long, from a 20-day chick embryo, continued in regular peristalsis for over 48 hours in the nutrient agar.

We have obtained growth in the nutrient agar containing from .9% to 1.58% of NaCl, 10% and 20% bouillon with .25% and .5% agar.

More recently still we have obtained active growth and migration of cells in a fluid medium as follows:

Ringer			
NaCl	.9	gm.	
KCl	.042	"	
$CaCl_2$	.025	"	5 cc.
$NaHCO_3$	.02	"	
H_2O	100	cc.	
Bouillon			5 cc.
NaCl			.045 gm.

The migrating cells in this fluid medium are often irregular with long slender processes almost exactly like those we have seen in plasma media. The cells are active, sending out and retracting their pseudopodia, and sometimes moving slowly apparently on the under side of the coverslip. Some of the transplanted pieces also show radiations.

Shorey reports the growth of nerve fibers of Necturus in a nutrient gelatin, but no notice of an active proliferation or migration of cells was contained in her description.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

Meeting of October 17, 1910.

Dr. Louis Hamman presiding.

Employment of Radium as an Aid to Surgery in the Treatment of Cancer, Angioma and Keloid.* Dr. Louis Wickham, Paris, France.

The destruction by burning, which is chiefly sought for by many radium-therapeutists, is not of great interest, since similar results can be obtained by many other agents.

The most interesting and important aspect of radium as a therapeutic agent is the selective action of the rays. Here radium plays the rôle of a subtle modifying agent, which goes to seek out those elements which are the most sentitive to its action. All morbid conditions are not suitable ground for this selective power; the most favorable are cancer, angioma, keloids, eczema, and other diseases.

The exact meaning of "selective action" is that a certain quantity of measured radio-activity can modify the cancerous cells and arrest their malignant evolution, without producing any modifying action on the normal cells surrounding the cancer, thus enabling a cancer to regress and disappear without producing on the surface any signs of irritation or inflammation.

This selective action can work either on the superficial or the deep seated pathological tissues, the rays possessing the power of traversing them. The determining cause between the caustic action which burns, destroys, and the selective action is the *quantity* of rays absorbed in a given time by the tissue. If large quantities of slightly penetrative rays be employed, the result is a superficial necrotic action; but if the quantity be measured, a selective action without any irritation can be secured.

If a large quantity of superpenetrative rays be used a deeper necrotic action follows, but let the quantity be measured, a selective action in the deep seated tissues without any irritation is the result.

Dr. Wickham here showed a series of lantern slides representing histological sections of fragments taken from a voluminous cancer of the breast (lobulated epithelioma) where the selective action of the rays was demonstrated. In this case this selective action was visible on fragments taken even from a depth of nine centimeters, a depth which, up to now, had not been deemed affectable by the radium rays.

The depth at which radium works depends on the quantity of radioactivity employed which in this case was 19 cgr. of pure radium applied for 48 hours at one point.

Dr. Wickham laid stress on the importance of acting simultaneously on, or in, several points of the tumor by his "crossfire" method in order to concentrate the greatest possible quantity of rays on the points in the deep-seated tissues so that the rays may act with greater homogeneity.

He showed, by means of lantern slides, cases, treated in collaboration with Dr. Degrais, of grave cancer, angioma, and keloids, in which the regressions were very remarkable.

The methods for the treatment of cancer by radium, that he has established with Dr. Degrais, joined to other methods of using radium as a therapeutic agent have led Dr. Wickham to the following conclusions:

* Abstract of a paper read before the Johns Hopkins Hospital Medical Society, October 17, 1910.

1st. The excellence of the results cannot exist without long experience and a profound knowledge of the methods to be used, and principally without a large quantity of radium.

2d. In the majority of cases surgery should be associated with the use of radium.

The radium-therapeutist, in the presence of a case of grave cancer, must first consult a surgeon in order that the patient may not be deprived of the prompt help of surgery.

If surgery is confronted with a case difficult or impossible to operate upon, radium can be applied *before hand*, in order to prepare the ground, or *afterwards* in combination with operative measures. Surgery ought to be utilized for making the perforations, incisions or partial extirpations which diminish the thickness of the tissues and render more effective the action of the radium introduced into the wounds.

Surgery should be also employed for opening a way for radium through artificial orifices or for conducting the tubes of radium to the tumors through the natural orifices. It is under such conditions that Dr. Wickham has treated cancers of the œsophagus, of the neck, of the bladder, of the intestines, of the rectum, of the larynx, of the uterus, subcutaneous and deep-seated cancers, cancers of the breast, etc. Dr. Wickham related the history of several cases of cancer which, normally would have succumbed in 2 or 3 months, but which are still, after one year, having their condition ameliorated. Surgery should develop its ingenuity for finding operative means of helping to apply the radium so that it will penetrate to the seat of the tumors, above all when these are of difficult access.

3d. The tumors should be inundated by the rays, and to this end the apparatus chosen should be the most powerful possible, and so numerous that the different radium containers may be employed in opposition, either on the exterior of the tumor, or in the interior after perforation. If there is any skin, mucous membrane, blood vessel, or nerve to protect, there must be placed between the apparatus and the tissues, metallic screens (aluminum, lead) whose thickness varies in proportion to the amount of radioactivity needed, and the duration of the application. This is the method of filtration that Dr. Wickham inaugurated in 1905, which is very useful when strong action in the depth of the tumor is needed, to prevent injuring the surface. The apparatus can be employed with very thin filters when it is important to utilize the maximum quantity of rays.

4th. Like surgery, radium has neither an action on the general physical condition, nor can it prevent recurrences and metastases. This should be insisted upon in order that the term cure, which on principle should be avoided, may be attributed only to the regression of the tumor itself, and so that there may be no risk of deceiving either the patient or the family physician.

5th. Even thus limited radium is a valuable weapon. In our struggle against cancer we are so badly armed that any new therapeutic agent if it be in some way really effective, as it is in this case, should be taken into serious consideration. By the help that radium brings to those suffering from cancer, it occupies a high place in our esteem and is the principal reason of the gratitude we owe to the discovery and scientific works of savants like Curie, Ramsay and Rutherford.

NOTES ON NEW BOOKS.

Practical Bacteriology, Blood Work and Medical Parasitology, Including Bacteriological Keys, Zoological Tables, and Explanatory Clinical Notes. By E. R. Stitt, M. D., Surgeon U. S. Navy, etc. Second edition. Revised and enlarged. Illustrated. Price $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

To the first edition, reviewed in the Bulletin, December, 1909, the author has added a chapter on Poisonous Snakes, and here and throughout the volume has incorporated new material, so that his work is as much "up to date" as possible. Dr. Stitt has crowded too much into this book—and this is its drawback—but it has merits which make it a useful aid to the student, who is willing to use it as a guide only, along with other standard textbooks.

The Harvey Lectures. Delivered under the Auspices of The Harvey Society of New York, 1909-10. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

The lectures by Prof. Richard M. Pearce on "The Problems of Experimental Nephritis," and by Prof. Eugene L. Opie on "Inflammation" have already appeared in the Archives of Internal Medicine, and that by Prof. Magnus-Levy on "Uric Acid in Gout," in the American Journal of the Medical Sciences. The other papers by Professors Huber, Cohnheim, Brodie, Hektoen and Meyer are here published for the first time. Three of these lectures, those by Pearce, Brodie and Huber, deal with problems relating to the kidney; in last year's series there were four on metabolism in connection with which Magnus-Levy's paper should be read. He and Prof. Cohnheim, who discussed "The Influence of Sensory Impressions on Scientific Deductions" were the two notable foreigners who appeared before the society. Dr. Meyer dealt with the much involved problem of "The Present Status of Aphasia and Apraxia," and Dr. Hektoen also treated a very complex subject in his lecture entitled, "On the Formation and Fate of Antibodies.

The Harvey lecturers contribute annually much that is of permanent value to medical science, and the addresses of the past year emphasize the importance of this society.

Treatise on Diseases of the Skin. For the Use of Advanced Students and Practitioners. By Henry W. Stelwagon, M. D., etc. Sixth edition. Thoroughly revised. Illustrated price, $6.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

Between June, 1902, and the present time this work has been reprinted ten times and revised six, which shows the exceptional, but well deserved, success it has had. The last edition is more abundantly and still better illustrated than its predecessors, and the author has added much new text on pellagra, sporotrichosis, oriental sore, gangosa, granuloma annulare and other rare affections, thus keeping his book well up with the latest developments in knowledge and treatment of these diseases. The third edition was reviewed in the Bulletin in August, 1904. What most prac-

titioners desire is a good practical book on skin affections, and in Stelwagon's they will find all the help that can be given them, for there are no diseases more trying than these to both doctor and patient, and none in which no help seems to be forthcoming at times, but with the author's guidance doctors can at least feel certain they are doing no harm, and as much good as anyone, if they make the right diagnosis. That is the difficulty in these diseases, but here also the author is clear in his descriptions, and the simpler affections should be easily recognized after studying his descriptions of them. The rarer ones, when met with, should be referred to a specialist. The book is in every respect thoroughly reliable.

American Edition of Nothnagel's Practice. Diseases of the Intestines and Peritoneum. By DR. HERMANN NOTHNAGEL, of Vienna. Edited with additions by H. D. ROLLESTON, M. A., M. D., F. R. C. P., etc. Second edition. Thoroughly revised. Price, $5.00. (*Philadelphia and London: W. B. Saunders Company, 1907.*)

The excellencies of this work were noted in the BULLETIN at the time of its first appearance (July-August, 1904), and this edition is an improvement on the first. It has been "thoroughly revised" and those already acquainted with Dr. Rolleston's work will be glad to have a chance to see how his views on many points, still awaiting solution, have been modified, and note the changes he has found it necessary to make. Students should be familiar with Nothnagel's Practice, which is a standard work.

Diagnosis and Treatment of Women. By HARRY STURGEON CROSSEN, M. D., Professor of Clinical Gynecology, Washington University, St. Louis, etc. Second edition. Revised and enlarged. Illustrated. (*St. Louis: C. V. Mosby Company, 1910.*)

The first edition of this work was reviewed in the BULLETIN for April, 1908. Since then the author has enlarged his book, and improved his index, and now more than ever the general practitioner will find the volume a most useful one.

Scientific Memoirs. By Officers of the Medical and Sanitary Departments of the Government of India. (New Series) No. 38. *Preliminary Report on the Killing of Rats and Rat Fleas by Hydrocyanic Acid Gas.* By CAPTAIN W. D. H. STEVENSON, M. B., I. M. S. (Bombay Bacteriological Laboratory.) Price 9d. (*Calcutta: Superintendent Government Printing, India, 1910.*)

The nature of this report is of such a special character that it will not appeal to many readers, but our health officers and others should read it, as all carefully studied means for exterminating the cause of plague should receive serious attention by them.

The Annual Report from the Chemical Works of E. Merck of Darmstadt (*Ger.*), which has just appeared, contains much interesting information "of recent advances in pharmaceutical chemistry and therapeutics." Eighty-five pages are devoted to "Serum Therapy and Bacteriotherapeutic Preparations," and about 250 to new preparations and drugs. The therapeutist and pharmaceutist, when desirous of information about the newest chemical preparations, will find this report a useful and reliable one.

The Modern Treatment of Alcoholism and Drug Narcotism. By C. A. MCBRIDE, M. D., L. R. C. P. & S. (Edin). Price $2. (*New York: Rebman Company, 1910.*)

Physicians in charge of sanatoria for the care and cure of inebriates, and others addicted to various drugs, will be glad to have this volume on their shelves. The author has had a very large experience, and his conclusions are therefore worthy of consideration. The book is brief, divided into six chapters as follows: 1, What is Inebriety; 2, Pathology; 3, The Causes of Inebriety; 4, The Forms of Inebriety; 5, Treatment; 6, Ether Inebriety, etc., and an Index. Perhaps the best chapter is the one on treatment and this is doubtless the one of most interest to the student of these troubles. The readers of this work should not be misled by the optimism of the author, which at times leads him, we feel, to exaggerations.

The Diseases of China, Including Formosa and Korea. By W. HAMILTON JEFFERYS, M. D., Medical Missionary in China, etc., and JAMES L. MAXWELL, M. D., Medical Missionary in Formosa, etc. Illustrated. Price $6. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

A couple of sentences from the authors' preface set forth clearly the nature and scope of this interesting work. "It is necessary to emphasize that this book is not in any sense intended to be a general text-book of medicine, nor even to cover the whole ground of the diseases met with in China . . . . Our aim is to present to medical men working in China, both Chinese and foreigners, a concise account of the special diseases they will meet with in their own practice in this Empire." This is a really valuable work, therefore, for all men intending to be missionaries, and there is also much information in it which is important to students elsewhere. The authors' statements in regard to syphilis and parasyphilitic affections should throw new light on the development of these obscure troubles. There is a picturesqueness about the work which is generally lacking in medical text-books and Drs. Jefferys and Maxwell are to be sincerely congratulated on the success of their task.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D., and LEIGHTON F. APPLEMAN, M. D. Vol. IV. December, 1910. (*Philadelphia and New York: Lea & Febiger.*)

A word only is needed to call attention to this last volume of the series which has appeared in the "Diseases of the Digestive Tract and Allied Organs, The Liver, Pancreas and Peritoneum—the Diseases of the Kidneys—Surgery of the Extremities, Shock, Anæsthesia, Infections, Fractures and Dislocations, and Tumors—Genito-urinary Diseases—Practical Therapeutic Referendum." The reviewers are Belfield, Bloodgood, Bradford, Landis and Lavenson, each of whom covers his territory so satisfactorily that no article of real importance on a given subject is overlooked, and there is careful weighing of the merits of each paper referred to.

Physicians Visiting List. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

Numberless physicians will find this pocket note-book, with its medical tables of incompatabilities, weights and measures, doses, etc., useful, and every physician should carry some such note-book. No one has a perfect memory and doctors should be especially careful to preserve notes and memoranda dealing with their patients. The 60th issue of this Visiting List shows that the publishers have gained a well-earned success with it.

The Care and Training of Children. By LE GRAND KERR, M. D., etc. (*New York and London: Funk & Wagnalls Co., 1910.*)

The author has written other works on babies and children, all marked by careful thought, and good judgment. This small, neatly printed volume is a helpful guide for young parents, and many older ones could also read it with advantage. Dr. Kerr talks simply and pleasantly about The Child's Room, Clothing, Diet, Bathing, Education, Punishment, Government of the Child, Child's Friends and Amusements, and other matters of importance to

the welfare of a child. The question of the correct up-bringing of children is a ever vital one, and this book is sure to lead some mothers and fathers to do better than they would have done without it.

Bismuth Paste in Chronic Suppurations—Its Diagnostic Importance and Therapeutic Values. By EMIL G. BECK, M. D. With an introduction by CARL BECK, M. D. And a Chapter on the Application of Bismuth Paste in the Treatment of Chronic Suppuration of the Nasal Accessory Sinuses and the Ear. By JOSEPH C. BECK, M. D. Illustrated. Price $2.50. (*St. Louis: C. V. Mosby Company, 1910.*)

Through articles in the medical journals Beck's original use of bismuth paste in this form of suppuration has been known for several years, and his practice has been followed with more or less success by many surgeons. At last in book form he presents his experience with this method of cure, and the profession will be grateful to him for it, since this is the first authoritative and full report on this subject which is of real importance in surgery. One of the values of this book is that it is not too long, and the matter is so well presented that its readers can easily read it through. Its essential importance is in making clear to practitioners the real and great values of bismuth when properly used in these surgical conditions.

The Dawn of the Health Age. By BENJAMIN MOORE, M. A., D. Sc., M. R. C. S., L. R. C. P. Price $1.40. (*London: J. & A. Churchill. Philadelphia: P. Blakiston's Son & Co., 1911.*)

Dr. Moore's object in writing this book, is, as explained in the preface, "to demonstrate on clear, broad lines, the necessity for entirely remodelling the present system of medical service, in the interests of the whole community." Much remodelling of medical service is necessary here as well as in England, and those interested in the larger problems of the profession will be glad to read this book, that they may see the difficulties, and study the cure proposed by the author. He suggests that all hospital appointments should be under the control of the State, and all doctors be paid by the State, so that there should be no rivalry amongst them, and so that the State might be better served. To stamp out tuberculosis he thinks the State should have the right to segregate all suffering from this disease until they died or were cured. Such radical measures do not seem feasible at the present moment, but who can foresee what changes will come about sooner or later in society, or what reforms a socialistic government might introduce.

Report of the International Commission on the Control of Bovine Tuberculosis. Reprint from 47th Annual Report of the American Veterinary Medical Association, September, 1910.

The Commission is composed of men well fitted by their knowledge and experience to deal with the problem under consideration, and their report evidences a careful review of the many factors entering into this difficult question. Their recommendations are made under four headings: (1) Education and legislation. (2) Location of tuberculosis. (3) Dissemination. (4) Disposition of tuberculous animals.

The recommendations under the head of education are very wise and practical and may be regarded as the first and most fundamental step in the entire campaign. Without intelligent coöperation on the part of the farmers, dairymen, butchers and consumers, legislation will fail.

The value of the tuberculin test is fairly defined and the recommendations for its use and safeguard from abuse are clearly set forth.

Until more widespread organization occurs—State Livestock Sanitary Boards, or other competent authority for wisely enforcing laws relative to bovine tuberculosis—little can be expected from legislative enactment.

The recommendations of means by which owners of herds can prevent their infection, or eradicate tuberculosis, or build up new herds free from tuberculosis are practical and deserve a more extensive trial than they have yet received in this country.

W. L. Moss.

Remedial Gymnastics for Heart Affections Used at Bad-Nauheim. Being a translation of "Die Gymnastik der Herzleidenden," von Dr. Med. Julius Hofmann und Dr. Med. Ludwig Pöhlman. Berlin und Bad-Nauheim. By JOHN GEORGE GARSON, M. D. Edin., etc. With fifty-one full-page illustrations and diagrams. Price $2. (*New York: Paul B. Hoeber, 1911.*)

With a few pages to explain the value and proper use of gymnastics in diseases of the heart, supplemented by photographs, with accompanying descriptions of the exercise shown, this book should appeal to many a practitioner, who has not had the chance to learn what gymnastic exercises can be safely practiced by a patient with heart trouble, and how his heart will be strengthened by them. But the physician must be able first to make a careful diagnosis of the condition of the patient, for a hap-hazard treatment of heart disease with gymnastics would quickly prove fatal in many a case. The diagnosis having been made then this work can be safely used, and can be recommended without danger.

Emanuel Swedenborg's Investigations in Natural Science and the Basis for his Statements Concerning the Functions of the Brain. By MARTIN RAMSTRÖM. University of Upsala, 1910.

The 200th anniversary of the University of Upsala has inspired an interesting review of the published and unpublished conceptions of one of the most remarkable men of the Swedish nation—Swedberg, later ennobled and renamed Swedenborg. Born in Stockholm January 25, 1688, be obtained his philosophical degree 1709, became assessor extraordinary of the Royal College of Mines 1716, was ennobled 1719, ordinary assessor 1724, retired 1745, and died in London March 29, 1772. A man of extraordinarily wide interests and wide opportunities, he has achievements in mathematics, in geology, neurology, chemistry, physics and cosmology, and finally he threw himself with intense zeal into anatomical and physiological studies which are published as "Œconomia Regni Animalis," dealing mainly with the blood, the brain and the soul. He foreshadowed the theory of epigenesis. His main interest in the brain lies in his emphasis of the "sphærula," or cerebellula of the cerebral cortex (now recognized as the cell-bodies), from which fibers arise and extend to medulla and cord and all parts of the body. The cortex is the seat of the sensorium commune and also of the motility. Each little cell lies in its own cavity and has its own fiber and a certain independence; but they also work together in groups; and he suggests that the relation of the convolutions to the one or the other muscle in the body could only be established on living animals by puncture, section and compression of the convolutions. He also accepted subordinate secondary motor centers for automatic and habitual movements in the medulla and cord. The soul in turn is localized in the cortex and if it were not for the difficulty about immortality he would identify it with the fluidum spirituosum of the cerebellula. "It amounts to the same thing if we see in this fluid the soul itself or only its faculty of imagination and judgment, for the one cannot be thought of without the other." In a manuscript, partly published in London, 1882 and 1887, under the title "The Brain," he extended his work and even developed the fact that in the motor representation in the anterior parts of the brain, the feet depended upon the highest parts, the abdomen and thorax on the middle and the face and head upon the third lobe.

In his historical study, Ramström aims to account for the foundation of Swedenborg's conclusions. The data seem to have

been literary, used with the intuition of a genius, but neither in him nor in his influence on the reader a spur to direct investigation.

Treatises of Fistula in Ano, Hemorrhoids and Clysters. By JOHN *Arderne.* From an Early Fifteenth Century Manuscript Translation. Edited with Introduction, Notes, etc., by D'Arcy Power, F. R. C. S. Eng. Price 15s. (*London: Kegan, Paul, Trench, Trübner & Co., and Henry Frowde, Oxford University Press, 1910.*)

Though the operative material of mediæval surgeons was necessarily quite limited in amount, no one can come away from their writings with anything but respect for the extensive knowledge they managed to accumulate with inadequate clinical methods. This is the feeling which Arderne's work awakens. Its phraseology is charmingly quaint; and it abounds in shrewd, wily advice, and a sly, though none too refined, humor. The author was a "type of surgeon who has happily never been absent from England—an English gentleman as well as a fine surgeon"; and much of what he writes has to do with the ethics of the profession: which is quite intelligible when one remembers the none too savory reputation of the surgeons of the day, and their methods, not always above reproach. He is strong for caution; advises against undertaking a case, except deliberately; always mentions the untoward results that may be expected; and insists on the surgeon having a definite understanding with the patient's relatives—even to an advance-collection of a portion of the fee—before an operation is done. If the emphasis laid on this sort of worldly wisdom seems out of proportion, one has to remember how precarious was the standing of the surgeon in these days; and to recall King John of Bohemia, who sewed up his French leech in a sack and threw him into the Oder because he had not cured his cataract as he had promised.

Arderne advised the operative treatment of fistula and devised needlessly cumbersome instruments for it; but the great advance he made seems to have been in the avoidance of the corrosive and irritating after-treatment used by every one else. Again and again he emphasizes the importance of letting wounds alone.

Hemorrhoids—which, unless they bled too profusely, he regarded as of use in preventing "mania, melancolia, pleuresis, ydropisy, passions of the spleen," etc.—were treated by local applications.

The Treatise of Arderne belongs to the series published by the Early English Text Society; and has been excellently edited by D'Arcy Power. The antiquated spelling, and many of the peculiarities of the original type have been retained. This has enhanced the attractiveness of the book; and though it has made it somewhat more difficult reading, the text has been rendered quite accessible by an excellent running commentary of marginal notes.

The Official Announcement of the University of Vienna about its Post-Graduate Medical Work, published by Urban and Schwarzenberg of Berlin and Vienna, will be sent to anyone on application to Rebman Company, New York, free of charge. This pamphlet is printed in German, but accompanied by an English and French translation, so that no prospective student need have any difficulty in understanding exactly the condition of post-graduate work in that university before going there.

Golden Rules of Ophthalmic Practice. By GUSTAVUS HARTRIDGE, F. R. C. S., etc. Golden Rule Series, No. VII. Fifth edition. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1910.*)

That this small work is very popular is shown by the appearance of its fifth edition. This series of "Golden Rules," volumes measuring only 4¼ by 2¾ inches, seems to have had marked success among English practitioners, and there is no doubt that the rules are well chosen, but there is danger that such books, no matter how well prepared, lead to superficiality of work. The practice of medicine cannot be regulated by hard and fast rules, even when "golden."

"Salvarsan" ("606") (Dioxy-Diamido-Arsenobenzol). Its Chemistry, Pharmacy and Therapeutics. By W. HARRISON MARTINDALE, Ph. D. Marburg, F. C. S., and W. WYNN WESTCOTT, M. B. Lond., D. P. H. Price $1.50. (*New York: Paul B. Hoeber, 1911.*)

The Treatment of Syphilis by the Ehrlich-Hata Remedy (Dioxydiamido-Arsenobenzol) A Completion of the Published Observations. By DR. JOHANNES BRESLER. Second edition. Much enlarged, with portraits of Ehrlich and Schaudinn. Translated by DR. M. D. EDER. With an Abstract of the Most Recent Papers. Price $1. (*New York and London: Rebman Company, 1911.*)

The work by Bresler supplements that of Martindale and Westcott to a certain extent, for even in theirs there is some account of the papers abstracted by him. Both books are useful and arrive at a most opportune moment when "606" is being put on the market. Practitioners must carefully study all the latest information on this subject and we recommend heartily "Salvarsan" in which they will find the proper methods of giving this drug set forth clearly, and its dangers noted. Martindale and Westcott have prepared an excellent manual, containing what is most essential for the instruction of the profession at large on this new remedy.

The Principles of Bacteriology. A Practical Manual for Students and Physicians. By A. C. ABBOTT, M. D., Professor of Hygiene and Bacteriology in the University of Pennsylvania. Eighth edition. Thoroughly revised. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1909.*)

The 8th edition of this well known book scarcely calls for extended comment. Naturally a large portion of the text is practically unchanged. As the author remarks in the preface: "The advances in bacteriology which have occurred since the issue of the 7th edition have been considerable, but not such as to affect materially the fundamentals essential to the education of the beginner." Parts of the book, however, have been rewritten, notably the chapter on infection and immunity, and the work has been brought up to date in other respects, as far as is compatible with the purpose it is intended to serve; namely, as a manual for students and practitioners of medicine.

A Handbook of the Surgery of Children. By E. KIRMISSON, Professor of the University of Paris; Surgeon to the Hospital for Sick Children, etc. Translated by J. KEOGH MURPHY, M. C. (Cantab.), F. R. C. S., etc. Price $7. (*Henry Frowde, Oxford University Press. Hodder and Stoughton, Warwick Square, E. C., 1910.*)

The author says he has left out all pure theory, history, pathological anatomy and pathogeny in order to insist on the knowledge of symptoms, diagnosis and treatment.

He divides all infantile surgery into two great subjects. Firstly, the study of malformations, and secondly, diseases connected with the locomotor apparatus. To these must be joined certain other affections such as appendicitis, mastoiditis, diseases of the throat, empyema, intussusception and lastly prolapse and polypi of the rectum.

The book is separated into four parts. Part I, 280 pages. Surgical affections of congenital origin which include, Congenital

Affections of the Back, the Head and the Neck; Congenital Malformations of the Trunk; Malformations of the Extremities. Part II, 75 pages. Injuries in Childhood. Part III, 418 pages. Inflammatory Lesions and Disorders of Nutrition, which are divided into Disorders of the Locomotor Apparatus: Affections of Different Regions. Part IV, 30 pages. Neoplasms or Tumors.

The chapter on anesthesia is by Cecil Hughes. He prefers chloroform, either alone or in mixtures, for anesthesia in children. This is interesting as the majority of anesthesias in this country are with ether, which is safer, in most instances.

The translator has used, as far as possible, the author's own words, and his work is nicely done. He has added a few well considered footnotes of his own.

The book is well gotten up and is profusely illustrated.

While some of the authors' ideas are at variance with those generally accepted nevertheless the book accomplishes its purpose, and will be a helpful addition to the other works on the surgery of children which have appeared in the last two years.

J. S. D

Bier's Textbook of Hyperæmia as Applied in Medicine and Surgery. By Professor Dr. August Bier, of Berlin. Only authorized translation from the sixth German revised edition. By Dr. Gustavus M. Blech, Professor of Clinical Surgery, Illinois Medical College. With thirty-nine illustrations. Price $4. (*New York: Rebman Company.*)

The chapter on the treatment of acute inflammation and suppuration has been changed and enlarged. Chapters on the treatment of keloids, tenosynovitis and diseases of the skin have been inserted. An index has also been added.

The work is well translated and nicely gotten up. There is an extensive bibliography throughout. The author takes up certain criticisms of his methods and demolishes them.

There is no doubt of the efficacy of hyperemia in a number of conditions, and we have all seen good results following its proper use, but the method is hardly a panacea as one might believe after glancing over the volume.

J. S. D.

The Vegetable Proteins. By Thomas B. Osborne, Ph. D., etc. Price $1.20. (*London, New York, Bombay and Calcutta: Longmans, Green & Co., 1909.*)

This little volume of about 100 pages by the well-known authority on vegetable proteins, Thomas B. Osborne, of New Haven, Conn., is one of the Monographs on Bio-chemistry edited by Plimmer and Hopkins. It is a clear, concise, carefully written exposition of the present state of knowledge in this somewhat confusing branch of chemistry. Dr. Osborne has himself been the chief contributor in this field for a number of years, and the book is, therefore, not merely a review of the work done by others, but an expression of his own views. Outside of Osborne's own laboratory comparatively little research on vegetable proteins has been carried out since the investigations of Ritthausen, which were not generally credited immediately after their publication, but which are now abundantly approved largely by the investigations of the author of this book.

The volume is divided into 11 chapters in which the occurrence of proteins in different parts of plants and their general characteristics, the isolation and separation of seed proteins and their reactions in respect to solubility, precipitation, denaturing and hydrolysis are considered with great detail. The classification of vegetable proteins which Dr. Osborne employs is based upon the work of the American committee on nomenclature, but at the same time the author points out that the American and English committees appointed to consider this subject are in practical uniformity in their views.

To the medical man the last chapter of the book in which such subjects as tox-albumens, anaphylaxis, precipitins and agglutinins are considered, is naturally the most interesting. The occurrence among plants of reactions which originally were seen with animal tissues is not without deep significance in view of the fact that many of the diseases in man may be traced to microorganisms belonging to the vegetable kingdoms.

The volume is furnished with a most complete bibliography of over 600 references in accordance with the wishes of the editors that each monograph should furnish a complete list of the papers previously published on the subject of which it treats.

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